Gynecologic Oncology Reports 24 (2018) 94–98

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case report

Next-generation sequencing based detection of germline and somatic alterations in a patient with four metachronous primary tumors

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ARTICLE INFO

Keywords:
Multiple primary tumors
Next-generation sequencing
Tumor mutational burden
Immunotherapy

ABSTRACT

Introduction: Multiple primary tumors (MPTs) are defined as two or more separate synchronous or metachronous neoplasms occurring in different sites in the same individual. These tumors differ in histology, as well as primary sites from which they arise. Risk factors associated with the occurrence of MPTs include germline alterations, exposure to prior cancer therapies, occupational hazards, and lifestyle and behavioral influences.

Case report: We present a case of a patient who was diagnosed with four metachronous primary tumors. In 2013, she was diagnosed with serous proliferations associated with psammomatous bodies of primary peritoneal origin (pT3NxM0). This was followed by invasive ductal carcinoma of the breast (stage pT2N0Mx, histological grade III/III) in 2014, melanoma (stage pT2bNxMx) in 2016 that further advanced to the lung and brain in 2017, and a low-grade lung carcinoid in 2017. To better understand the biology of this patient's MPTs, we performed next-generation sequencing (NGS) to assess for both somatic and germline alterations. The treatment course for this patient aims to target the tumor with the strongest prognostic value, namely her malignant melanoma, and has contributed favorably to the overall survival of this patient.

Conclusion: We report the clinical and genomic landscape of a patient with MPTs who had no identifiable unique somatic or germline mutations to explain her predilection to cancer. The treatment course and overall prognosis for this patient is important for understanding future cases with unrelated, metachronous MPTs, the occurrence of which cannot always be explained by underlying genetic mechanisms.

1. Introduction

Multiple primary tumors (MPTs) are defined as two or more separate synchronous or metachronous neoplasms of different primary disease site and histology. Due to an increase in cancer screening and prevention efforts, along with an improvement in overall life expectancy, there has been a consequent increase in the prevalence of MPTs. The incidence of MPTs is currently 2–17% (Vogt et al., 2017), and risk factors include germline alterations, exposure to prior cancer therapies, occupational hazards, and lifestyle influences (Vogt et al., 2017).

1.1. Case report

We present a 73-year-old woman with a medical history of Center of Disease Control (CDC) class 3 obesity (body mass index [BMI], 40 kg/m^2) and a family history of bladder, colon and lung cancers. In January 2011, she presented with post-menopausal vaginal bleeding that was refractory to multiple dilatation and curettages and hormonal therapy. An endometrial biopsy revealed focal complex hyperplasia without atypia. Pelvic ultrasonography and a computed tomography (CT) scan of her abdomen revealed no significant pathology. In November 2012, she underwent a diagnostic total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pathology revealed low-grade serous proliferation associated with psammomatous calcifications involving the

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https://doi.org/10.1016/j.gore.2018.04.004
Received 1 March 2018; Received in revised form 13 April 2018; Accepted 16 April 2018
Available online 18 April 2018

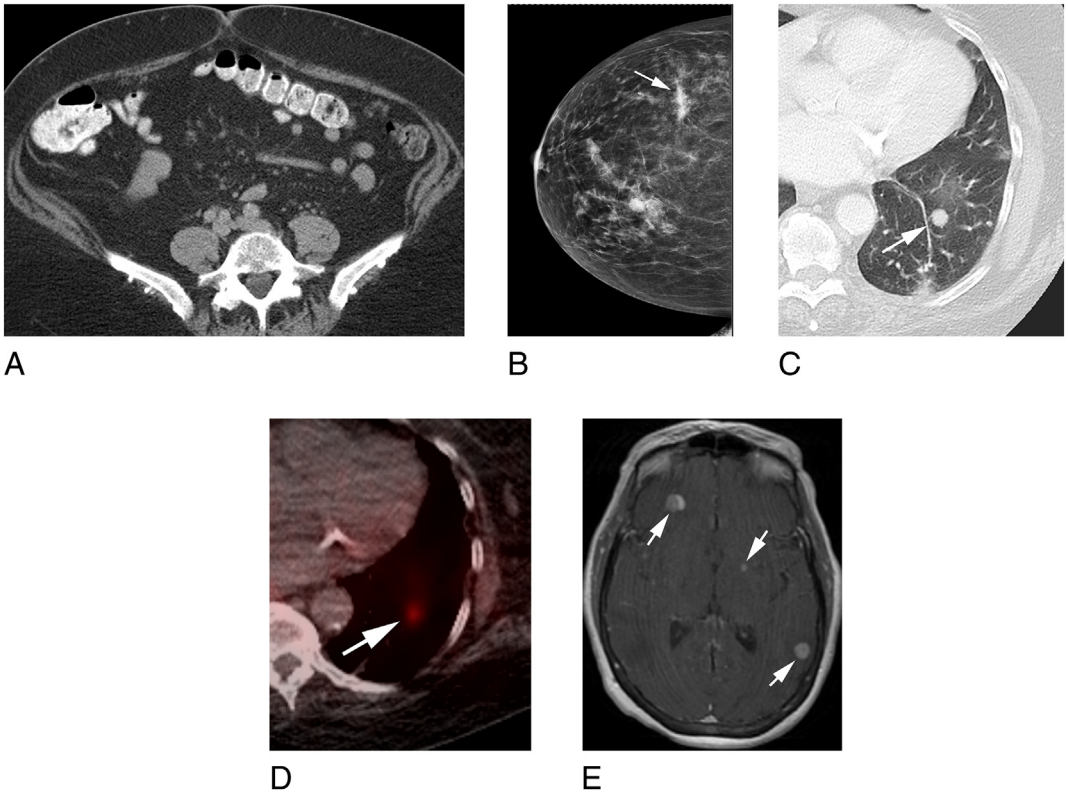

Fig. 1. A Axial computed tomography (CT) images of the pelvis demonstrating small foci of soft tissue nodularity in the omentum (arrows) consistent with carcinomatosis. B. Right mammogram craniocaudal projection demonstrating an irregular high-density mass in the lateral breast (white arrow) consistent with biopsy-proven invasive ductal carcinoma. An equal density mass with indistinct margins is present 1.6 cm anterior to thr dominant mass, consistent with a biopsy-proven satellite lesion. Circumscribed masses with markers in place were benign. C. Axial CT images of the left chest demonstrating a 1.1-cm solid left lower lobe lung nodule (arrow). D. Axial fused images from a Gallium 68 Dotatate positron emission tomography (PET)/CT demonstrating increased tracer accumulation in the left lower lobe nodule (arrow) consistent with carcinoid tumor. E. Axial T1-weighted gadolinium-enhanced magnetic resonance images of the brain demonstrating bilateral enhancing brain metastases (arrows).

uterine serosa and bilateral fallopian tubes with papillary tubal hyperplasia and associated psammomatous calcifications, consistent with a primary peritoneal origin. In May 2013, the patient reported ongoing abdominal pain, and an interval CT scan of her abdomen and pelvis (Fig. 1A) revealed subtle peritoneal nodularity, suspicious for peritoneal carcinomatosis as well as scattered subcentimeter pulmonary nodules at the lung bases. Omental biopsy revealed low-grade serous proliferation with psammomatous calcifications. In August 2013, she underwent a laproscopic omentectomy with multiple peritoneal biopsies, which confirmed a pT3NxM0 low-grade serous proliferation with psammomatous calcifications involving fibroadipose tissue in the omentum and peritoneal biopsy masses (Fig. 2A). No adjuvant systemic therapy was recommended, and the patient was monitored with interval cross-sectional imaging.

In July 2014, a routine mammogram revealed an asymmetrical density in the right breast (Fig. 1B). A core needle biopsy of the right breast confirmed an invasive ductal carcinoma. She subsequently underwent a right lumpectomy and a sentinel lymph node biopsy. Pathology revealed invasive ductal carcinoma, pT2N0Mx, stage IIA (Fig. 2B). The tumor was estrogen receptor/progesterone receptor (ER/PR) positive and human epidermal growth factor receptor 2 negative. She was started on adjuvant anastrozole, an aromatase inhibitor, and remains without evidence of recurrent disease.

In May 2016, the patient presented with a bleeding ulcerated lesion on her back. A biopsy revealed an ulcerated malignant melanoma measuring 1.7 mm in thickness, with numerous mitoses. A wide resection identified an additional 0.4 mm melanoma, pT2bNxMx, stage IIB. The patient did not receive adjuvant systemic therapy.

In April 2017, surveillance imaging revealed a new 0.7-cm nodule in the left upper lobe, as well as increasing bilateral pulmonary nodularity at the lung bases, the largest nodule measuring 1.1 × 1.0 cm, initially 0.5 × 0.4 cm in 2013, concerning for possible metastatic disease (Fig. 1C). A biopsy of the dominant left lower lobe lung nodule revealed a carcinoid tumor with spindle cell features (Fig. 2C). The Ki67 proliferative index was < 5%, and no mitoses or necrosis were identified, consistent with a low-grade primary carcinoid of the lung. Staging positron emission tomography revealed multiple bilateral pulmonary nodules without any extrathoracic foci of disease (Fig. 1D). As the patient was asymptomatic from her pulmonary carcinoid, she was placed under observation.

In July 2017, routine surveillance CT of the chest, abdomen, and pelvis revealed that a left lung nodule had increased in size. Given her history of MPTs, a repeat biopsy of the lung nodule was performed, revealing metastatic melanoma (Fig. 2D). In July 2017, she initiated systemic therapy with pembrolizumab. In August 2017, she noted persistent headaches and magnetic resonance imaging of the brain revealed innumerable brain metastases, presumed metastatic melanoma (Fig. 1E). Subsequently, immunotherapy was switched to ipilimumab and nivolumab given improved central nervous system response. As of March 2018, she remains on ipilimumab and nivolumab with ongoing clinical and radiologic response to therapy.

We performed next-generation sequencing (NGS) of all available tumor tissue to assess for somatic (Table 1) and germline alterations (Table 2) in the hopes of identifying an underlying etiology of her MPTs. We performed hybridization capture and deep-coverage NGS to detect somatic mutations in 468 somatic cancer-associated genes as well as 75 germline alterations. All mutations were called against the patient's matched normal sample, and the mean overall coverage of