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Case Report

Metachronous and Synchronous Occurrence of 5 Primary Malignancies in a Female Patient between 1997 and 2013: A Case Report with Germline and Somatic Genetic Analysis

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Abstract
The number of patients with multiple primary malignancies has been increasing steadily in recent years. In the present study, we describe a unique case of an 81-year-old woman with 5 metachronous and synchronous primary malignant neoplasms. The patient was first diagnosed with an endometrium adenocarcinoma in 1997 and a colon adenocarcinoma in 2002. Eleven years after her colon surgery, in 2013, the patient presented with 3 other primary ma-

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lignancies within a 4-month time span: an invasive malignant melanoma on the lower leg, an invasive mucinous breast carcinoma in the right breast, and a pleomorphic spindle cell sarcoma on the left upper arm. Subsequent routine medical checkups in 2013–2017 revealed no metastases of the primary malignancies. The patient mentioned a familial aggregation of malignant tumors, including 2 sisters with breast cancer and a brother with lung cancer. Interestingly, next-generation sequencing analysis of the patient's blood sample detected no mutations in the *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *PALB2*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, *MUTYH*, *STK11*, *BMPR1A*, *SMAD4*, *PTEN*, *POLE*, *POLD1*, *GREM1*, and *GALNT12* genes. Therefore, whole genome sequencing is warranted to identify cancer-related genetic alterations in this patient with quintuple primary malignancies.

Introduction

Overall survival rates for cancer patients have improved tremendously during the past 40 years, in part due to individually tailored therapies [1]. As cancer patients live longer, there is an elevated risk of developing additional primary malignancies in other organs. Shared etiology and genetic, epigenetic, and treatment-related causes may contribute to malignant comorbidity, where a common early genetic event might have initiated their development. However, multiple malignancies might occur at different time points, with a few years' shift between them, indicating a longer latency period.

Breast cancer patients, mostly in Europe and the USA, have a 23–40% increased risk of a second primary malignancy (not including contralateral breast cancer) after hormone therapy (gynecological malignancies), chemotherapy (leukemia), and irradiation (lung cancer, sarcoma of thorax and upper limb, esophagus cancer, thyroid gland carcinoma) [2]. Moreover, women with bilateral breast cancer have a 1.5 times higher risk of developing some breast cancer-related malignancies [3]. Due to the cumulative effect of adjuvant treatment for several primary malignancies (previously administered radio- and/or chemotherapy), these patients will require individualized treatment strategies to avoid excessive cytotoxic harm. Here, we report a case of an 81-year-old female with 5 primary malignancies diagnosed as metachronous and synchronous tumors within 16 years, followed by genetic mutation analysis.

Case Report

An 81-year-old woman was diagnosed with 5 different primary malignancies during a 16-year period between 1997 and 2013. Interestingly, malignant tumors were detected non-simultaneously in several of her family members, suggesting a potential family cancer syndrome. Five of 10 siblings had been previously diagnosed with some form of malignancy, including 2 sisters over 60 years of age with breast cancer, a brother diagnosed with colorectal cancer, and another brother that died of metastatic cancer in the liver and lungs, where colon cancer was suspected as the primary tumor. In addition, 2 uncles were also diagnosed with some type of gastrointestinal malignancy, but neither her parents nor her 3 daughters were diagnosed with any malignant tumors.

The patient was diagnosed with her first malignancy in 1997 at the age of 61: an endometrium adenocarcinoma without lymph node metastasis. She underwent hysterectomy and

bilateral salpingo-oophorectomy. In 2002, an invasive, moderately differentiated adenocarcinoma (group B according to Duke's classification) in the colon ascendens was detected with no lymph node metastasis. In 2013, 3 different malignancies were detected, including a malignant melanoma of the left leg (Clark level II, Breslow 0.3 mm) at the pretibial region, a pleomorphic spindle cell sarcoma (40 mm large, grade 3 according to Trojani) in the left musculus biceps, and a 17-mm large invasive mucinous carcinoma in her right breast. The histological grade of the breast tumor was 2 (score 6 according to Bloom-Richardson-Elston scoring, with tubule formation 3, nuclear pleomorphism 2, and mitotic activity 1). Furthermore, the breast tumor was positive for the estrogen (100%) and progesterone (100%) receptors. The Ki-67 proliferation index was less than 10% and the Hercep test was negative. No metastases were found in 2 sentinel nodes from the right axilla (Fig. 1). The patient received adjuvant radiation and antihormonal therapy (Tamoxifen). The patient was still recurrence free 4 years after her breast surgery and had not developed metastases from any of the 5 primary tumors.

Materials and Methods

Genetic mutation analysis was performed in the clinical setting using EDTA blood samples, as previously described [4]. The study was approved by the Local Scientific Ethics Committee in Gothenburg (Dnr: 287-15).

In brief, the blood DNA sample was fragmented by ultrasonication, and custom SureSelectXT library kits (Agilent) were used to capture fragments from target genes in gene panels including the *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *CDH1*, *PALB2*, *RAD51C*, *RAD51D*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, *MUTYH*, *STK11*, *BMPR1A*, *SMAD4*, *PTEN*, *POLE*, *POLD1*, *GREM1*, and *GALNT12* high-risk cancer genes. The patient sample was analyzed with respect to possible mutations in the coding regions and splice sites. DNA sequencing was performed on the HiSeq 2500 (Illumina) with 2 × 100-bp paired-end reads. Raw sequencing data went through demultiplexing, alignment, PCR duplicate removal, variant calling, and annotation. Variants located in coding exons and 20 bp of adjacent introns were evaluated for pathogenicity. Copy number variations affecting one or more exons of the target genes were identified using an in-house method based on the number of read pairs in short windows over the target regions. Deletions and duplications were inspected in Integrative Genome Viewer (Broad Institute) to identify breakpoints. For analysis of large deletions and insertions in the genes, next-generation sequencing data were used, except for *PMS2* where multiplex ligation-dependent probe amplification was performed. Variants detected with next-generation sequencing were confirmed with Sanger sequencing. Only mutations/variants class 3–5 were reported. Interestingly, no mutations were detected in any of the analyzed genes. These findings demonstrate that whole genome sequencing is warranted for this particular patient with quintuple primary malignancies.

Discussion

Multiple primary malignancies (MPMs) were first described by Billroth [5] in 1889, followed by Warren and Gates [6] in 1932 and Moertel [7] in 1977, as the coexistence of at least 2 unrelated primary malignancies in a single patient. Depending on the time interval between the diagnosis of the first and second primary malignancies, MPMs are classified as

metachronous (more than 6 months apart) or synchronous (simultaneously or within 6 months of each other). However, it is important to verify that the multiple malignancies represent primary tumors and not metastases. Immunohistochemical evaluation of the tumor tissue is an effective method to exclude the existence of metastases and confirm the presence of MPM.

Here, we describe a case of an 81-year-old woman who had been treated for 5 different primary malignancies during a 16-year period. The majority of the patient samples were either early-stage malignancies without lymph node metastases (endometrium adenocarcinoma, colon adenocarcinoma, malignant melanoma) or neoplasms associated with a relatively favorable prognosis (mucinous breast carcinoma). Genetic analysis of the patient's blood sample using DNA sequencing revealed no mutations in genes associated with hereditary cancer syndromes (e.g., *TP53* or *BRCA* mutations). These findings are understandable, as her first malignant tumor was detected after the age of 60 and indicates a low penetrance. Furthermore, none of the 5 tumors were therapy-related malignancies, such as neoplasms that develop after radiation or chemotherapy administration.

The cumulative risk of multiple malignancies in this patient was estimated using data from the Swedish National Board of Heath for the cumulative risk per diagnosis per patient (up to 75 years of age). The cumulative risk per diagnosis was then multiplied for the 5 malignancies, resulting in a cumulative risk of 1.5×10^{-9}. These data suggest that other risk factors, e.g., inherited mutations, contributed to the development of the 5 malignancies in this patient than would be expected by chance.

Relatively few studies have been reported cases of 5 or more MPMs in different anatomical sites and only 1 study to date has performed genetic analyses of the patient sample. Castro et al. [8] recently reported a case of a patient with synchronous breast and pancreatic cancers where germline and somatic genetic analysis was performed showing a germline *BRCA2* mutation. Although the patient reported here had several family members with breast cancer and the patient herself had multiple cases of breast and gynecological cancer (metachronous endometrium adenocarcinoma and mucinous breast carcinoma), no mutations in the *BRCA1* or *BRCA2* genes were found in her blood sample.

A unique case was recently reported with 5 simultaneous primary malignant tumors (malignant melanoma of the right popliteal fossa and her right arm, an invasive lobular breast carcinoma, diffuse large B-cell lymphoma, nodular lymphocyte predominant Hodgkin lymphoma and a giant cell tumor of left tibial soft tissue in tendon sheath/pigmented villonodular synovitis) in a 57-year-old woman [9]. However, 2 of the patient's 5 tumors were hematopathological malignancies. Zhao et al. [10] recently reported about a female patient with the highest number of primary malignancies. The patient developed 8 primary malignant neoplasms in 4 different anatomical sites (6/8 tumors originated in the gastrointestinal tract), 5 of which were diagnosed in the colon. The other neoplasms originated in the breast, endometrium, and small intestine. Both cases were of particular interest due to the high number of multiple malignancies per patient, but neither case reported tumors in completely independent organs as was found in the present study.

Two recent publications have reported cases of breast cancer in men with multiple malignancies. Male breast cancer is relatively rare, particularly when diagnosed with other multiple malignancies. Rastogi et al. [11] reported a male patient with triple primary malignancies including breast, esophagus squamous cell carcinoma, and tongue squamous cell carcinoma. Zargar-Shoshtari et al. [12] also published a case report of a male breast cancer patient with metachronous malignancies in the kidney and prostate gland.

Few case reports on MPM have also evaluated the genetic background of the patient. In general, genetic analyses are recommended for patients with several primary malignancies, as immediate family members (e.g., siblings, children and grandchildren) may be affected. If family members are aware of their elevated risk of developing a particular type of cancer due to genetic predisposition, surveillance is warranted. For instance, in families where malignant melanoma or breast carcinoma is common, regular dermato-oncological check-ups/sunbathing restrictions or regular mammography screening could be done, respectively. Furthermore, if a patient with MPM is positive to genetic counseling, it may help other family members to join genetic testing for cancer risk assessment.

Second malignancies diagnosed in a different organ have been previously considered to be a metastasis. Using histopathological and immunohistochemical analyses has helped to establish more accurate diagnoses of second primary malignancies, which in turn can affect treatment strategies and patient outcome prediction as patients with primary tumors frequently have better prognoses than metastatic patients. Additionally, second malignancies that occur in long-term survivors may be due to sporadic cancers that would have occurred anyway, where environmental, genetic, reproductive, and lifestyle factors (smoking, alcohol consumption, and body mass index) may play a role.

In summary, identifying the type of different synchronous and metachronous primary malignancies may awaken a special clinical vigilance for oncologists, warranting new screening programs (e.g., *BRCA1/2*) for cancer patients to detect other primary malignancies at an early stage. Patients with several primary malignancies are in need of special treatment strategies (including longer follow-up), regarding the previously administered radio- and/or chemotherapy, to avoid excessive cytotoxic harm due to the cumulative effect of adjuvant treatment for several primary malignancies.

Since none of the high-risk genes (e.g., *BRCA, TP53*) were mutated, whole genome sequencing is warranted to detect possible low-penetrant genes in our patient and in her family members.

Statement of Ethics

Informed consent was obtained from the patient.

Disclosure Statement

The authors have no potential conflicts of interest to disclose.

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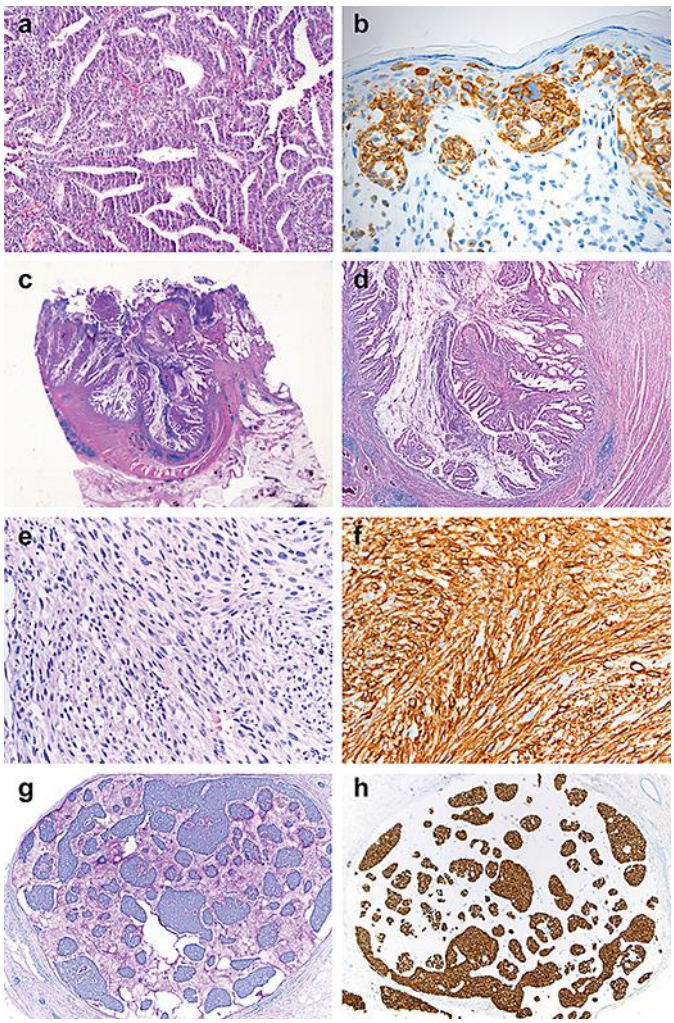

Fig. 1. Hematoxylin and eosin (H&E) and immunohistochemical staining in 5 primary malignancies from the patient. **a** Invasive moderately differentiated adenocarcinoma in the endometrium. H&E staining. Magnification, ×100. **b** Invasive malignant melanoma of the left leg (Clark level II, Breslow 0.3 mm) at the pretibial region. Melan-A immunohistochemical staining. Magnification, ×400. **c**, **d** Invasive moderately differentiated adenocarcinoma in the colon ascendens. H&E staining. Magnification, ×5 (**c**), ×20 (**d**). **e–f** Spindle cell and pleomorphic cell sarcoma (grade 3 according to Trojani) in the left musculus biceps. H&E staining and α-SMA immunohistochemical staining. Magnification, ×200. **g–h** Invasive mucinous breast carcinoma (grade 2). McManus staining and estrogen receptor immunohistochemical staining. Magnification, ×40.