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Recurrent melanoma development in a Caucasian female with CDKN2A+ mutation and FAMMM syndrome: A case report

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Abstract

Melanoma is a form of skin cancer originating from melanocytes that has an increasing incidence over the past few decades. From 1992 to 2010, the overall incidence of melanoma was 12.29 cases per 100,000 person-years in Canada. Approximately 10% of cases are attributed to a hereditary component, with one of the most common being familial atypical multiple mole melanoma syndrome. In this case report, we highlight the atypical case of a middle-aged Caucasian female with familial atypical multiple mole melanoma syndrome, who has developed dozens of primary melanomas over the past decade. We highlight the management of her case, as well as the importance of monitoring by multiple other subspecialists given the propensity for the development of alternate malignancies.

Keywords

Familial atypical multiple mole melanoma syndrome, melanoma, CDKN2A mutation

Introduction

The incidence of melanoma has been increasing over the past few decades, and it is estimated that over 250,000 new cases are reported annually across the world.[1] From 1992 to 2010, the overall incidence of melanoma was determined to be 12.29 cases per 100,000 person-years in Canada.[2] Approximately 10% of these cases are believed to have a hereditary component, with one of the most common forms of hereditary melanoma being familial atypical multiple mole melanoma (FAMMM) syndrome, also known as dysplastic mole syndrome or atypical mole syndrome.

FAMMM syndrome is an autosomal dominant condition in which individuals are predisposed to melanoma development. Approximately half of these individuals also have a mutation in the CDKN2A (cyclin-dependent kinase inhibitor 2A) gene on chromosome 9, which is responsible for encoding p16 and p14arf, two tumor suppressor genes that regulate cell cycle progression.[3] Patients with FAMMM syndrome and a CDKN2A mutation have previously been estimated to have between a 50% and 85% chance of developing melanoma over the course of their lifetime.[4]

In this report, we highlight an atypical case of FAMMM syndrome in a middle-age Caucasian female who persistently continues to develop biopsy-proven primary melanoma despite constant surveillance and excision and who subsequently developed breast cancer. Our case is unique in that our patient has developed over 50 primary melanomas over the past decade; at the time of this writing, we were unable to find any case of FAMMM syndrome with development of this number of primary melanomas.

Case report

We first met our patient, J, approximately a decade ago, at the age of 32. She provided written consent for publication of this case report. Initially, she presented with a suspicious lesion which was removed and determined to be a Clark's level 3 melanoma. A few months later, she presented with two additional suspicious lesions, one on the mid-back and

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one on the shoulder. These lesions were excised, and both were pathologically confirmed to be melanomas in situ. Over the next few years, J continued to develop multiple biopsy-proven primary melanomas. We also discovered that she had a strong history of melanoma in the family on her maternal side—her mother passed away at the age of 40 from melanoma, her maternal grandfather at the age of 36, and her maternal aunt in her 40s. Genetic testing revealed J to have a c.225_243del19 mutation on the CDKN2A gene on chromosome 9. This specific mutation has been previously referenced as the p16-Leiden mutation given the fact that it results in a nonsense mutation in p16 tumor suppressor gene and that its origin can be traced back to a common ancestor from the early 18th century near the town of Leiden, Netherlands.[5]

In late 2011, J developed multifocal invasive ductal carcinoma with multiple lymph node involvement. Pathological testing revealed the cancer to be ER-/PR-/HER2+ and was staged as T2N2M0. She ultimately underwent a mastectomy and FEC-100 chemotherapy followed by docetaxel and trastuzumab as curative-intent treatment.

Our patient has since continued to have melanoma development at multiple different sites in various regions of her body, with no apparent pattern of distribution or development. We have continued to remove suspicious lesions, with over two dozen confirmed primary melanomas removed over the past 5 years alone and a total of over 100 lesions removed since her first presentation to our clinic. Many of these lesions appear innocuous on clinical examination.

Discussion

Patients with FAMMM syndrome and a CDKN2A mutation are at a substantially higher risk for melanoma development; however, the vast majority of patients tend to develop it only at a few primary sites.[6] J is remarkable in that she continues to develop primary melanomas, most of which are only a few millimeters in diameter, despite our continued excisions. Studies have suggested that patients who develop multiple primary melanomas tend to have the worst long-term prognoses due to malignancy; in J's case, she has multiple relatives who succumbed to melanoma in their 30s and 40s.[7]

Patients with CDKN2A mutations also tend to be at increased risk for development of alternate malignancies, such as those involving the lung, breast, and pancreas. This can most likely be attributed to the fact that one of the protein products of the CDKN2A gene is p16, an important tumor suppressor gene that regulates cell cycle progression and is widely expressed in a variety of cell types. Mutations in p16 have been heavily implicated in carcinogenesis and are frequently found in human cancers.[8] In our patient's specific case, the p16-Leiden mutation has also previously been implicated in increased risk for development of pancreatic cancer.[5] In fact, a previous study determined the relative risk (RR) of developing pancreatic cancer in patients with J's specific mutation to be 47.8, with an overall RR of developing nonmelanoma malignancy of 4.4, when compared with those without the mutation.[5] There is also a genetic link to breast cancer, as CDKN2A+ carriers have a RR of 2.95 compared with non-carriers in developing breast cancer.[5]

The biochemical mechanism behind the development of pancreatic cancer is unknown; however, studies have shown there to be a 15%–20% chance of developing pancreatic cancer by age 75, which is substantially higher than the general population. To the best of our knowledge to date, none of J's family members have ever developed pancreatic cancer.

Given the substantially increased risk, screening for pancreatic cancer is the standard of care for patients with known germline mutations for melanoma. Despite this, we were unable to find conclusive guidelines as to whether entire families with CDKN2A mutations should undergo screening. In the case of our patient, J has seen a gastroenterologist who has recommended annual pancreatic magnetic resonance imaging (MRI) screening. At the time of this writing, J had undergone two abdominal MRIs: one in early 2017, with a repeat in mid-2018. Both of these MRIs were unremarkable. From a dermatological standpoint, we are attempting to maintain ongoing follow-up of our patient every 2–3 months indefinitely given the unpredictable course of her disease. As of the most recent clinic visit in November 2019, no additional concerning lesions were identified on full skin examination.

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Informed consent

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