IJCMCR Open Access

ISSN 2692-5877
DOI: 10.46998/IJCMCR.2020.01.000024

International Journal of
Clinical Studies & Medical Case Reports

Case Report

The Challenging PMS2 Gene Mutation and its Role in Cancer Survivorship

Deborah J. Manst , MD, MPH[1]*† and Susan Hong, MD, MPH[1]†

[1]University of Illinois Cancer Center, Chicago, Illinois, USA

†Both authors significantly contributed to the content of this manuscript.

***Corresponding author:** Deborah J. Manst, MD, MPH, University of Illinois Cancer Center, Chicago, Illinois, 818 S Wolcott St, Rm 423, MC 709, Chicago, IL 60612, USA. Tel: (312) 355-8091; E-mail: manst@uic.edu

Received: June 20, 2020 Published: July 08, 2020

Abstract

Cancer survivorship care involves long-term follow-up of survivors including the management of risk for developing additional cancers. Evaluation for risk factors, including genetic predisposition to cancer, is an important component of this care. All cancer patients should undergo complete assessment of their family history and be referred for genetic counseling and testing when appropriate. Universal tumor testing has been advocated for some cancers where somatic mutations may correlate with germline genetic information, like colorectal and endometrial cancer. In addition, genetic analysis can identify patients who are likely to have Lynch Syndrome, a common form of hereditary cancer that elevates cancer risk and warrants preventive management.

Key words: Genetic Testing; Mutation; PMS2 Gene; Prevention; Cancer Survivorship

Introduction

Lynch Syndrome (LS) is one of the most common causes of hereditary cancer that elevates lifetime risks for developing colorectal, endometrial, ovarian, or numerous other types of cancers [1]. Several genes are associated with LS, including PMS2, which accounts for less than 10% of all LS mutations. However, mutations in PMS2 can double the lifetime risk for colorectal cancer (CRC) and elevate the risk for endometrial cancer (EC) by more than five times [2,3]. Universal testing of somatic tumor tissue for CRC and EC is now common. Testing is performed by immunohistochemistry (IHC) or microsatellite instability (MSI) analysis [4]. If tumor testing is abnormal, genetic counseling and testing is recommended. If germline testing confirms LS, patients can be appropriately managed with high risk screening and/or risk reducing strategies. We present a case of a woman with EC who was found to have a PMS2 mutation in her tumor.

Case History

The patient is a 48-year-old African American woman diagnosed with EC in 2017 at age 45. Biopsy performed for abnormal uterine bleeding showed endometrioid adenocarcinoma with loss of PMS2 nuclear expression by IHC testing. She underwent total hysterectomy, bilateral salpingo-oophorectomy, and regional lymphadenectomy.

Her family history was significant for cancer on both her maternal and paternal side. On her mother's side, an uncle had lung cancer in his 50s, a cousin had lymphoblastic lymphoma as an infant, and a first cousin once removed had an unknown cancer in her late 30s. Paternally, an uncle had CRC diagnosed in his 60s, a great aunt had breast cancer at an unknown age, a female cousin had breast cancer in her 50s, and a female second cousin had breast cancer at age 27. There were no cases of EC in either lineage.

Given her young age at diagnosis and loss of PMS2 on initial pathology, she was referred for genetic counseling and testing. Testing was performed via the OvaNext panel from Ambry Genetics, which assesses 25 genes including the LS-associated genes. Final germline genetic results were negative for mutations in any of the genes tested. However, due to complexities with PMS2 germline testing, guidelines from the National Comprehensive Cancer Network (NCCN) at the time recommended managing patients with conflicting tumor and germline testing as if they have LS. She was advised that she should screen for cancer with annual colonoscopy and upper endoscopy every two to three years.

In 2019, she presented to the cancer survivorship clinic, at which time she was reassessed for LS based on the conflicting data of her positive tumor testing and negative germline test results. Since her initial genetic counseling visit, NCCN guidelines were revised to recommend management based on family history. She had only one second degree relative with CRC in their 60s, which does not confer elevated risk, so she was advised that she no longer needed annual colonoscopies or upper endoscopies.

Discussion

Here we present a patient with EC with an abnormal PMS2 on IHC of tumor pathology, suggestive of LS, but with subsequent negative genetic testing. This approach of endometrial and colorectal tumor screening starting with IHC or MSI and

followed by germline confirmation was published in 2009 by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. EGAPP reports sensitivity of IHC in identifying LS to be 83%. Genetic sequencing of the PMS2 gene, however, has been complicated by technical complexity and only became available in 2009 [5].

Two possibilities could explain the discordance between the somatic and germline genetic test results in this patient. First, the patient may have a germline mutation in PMS2 that this test was unable to identify. This is possible for PMS2, as there is a nearly perfect homologous sequence, or pseudogene, downstream of the PMS2 gene that is not associated with LS. This may give false negative or false positive test results making appropriate cancer risk management unclear [6]. Second, the PMS2 mutation may be limited to somatic tumor tissue only. Although such individuals do not have a germline PMS2 mutation, the somatic tumor tissue acquires the PMS2 defect resulting in abnormal IHC staining. These patients do not have LS.

At the time of the patient's cancer diagnosis, guidelines recommended to follow-up abnormal tumor testing with genetic counseling and testing. Given the concern for false negative results, recommendations included following intensive cancer screening for patients with abnormal tumor testing and negative germline testing [7]. As genetics is a rapidly evolving field, these guidelines frequently change. More recent recommendations from the NCCN note several studies that show 45-68% of discordant results between somatic tissue and germline are due to mutations in the tumor tissue only, decreasing false negatives [8]. With this new information, cancer screening recommendations may be scaled back for some patients.

We re-evaluated this patient's genetic testing results and were able to deescalate her cancer screening. As a result of her survivorship visit, she no longer requires intensive and invasive screening, significantly impacting not only healthcare costs, but also her mental and physical health and financial well-being.

This case study emphasizes the need for continued surveillance of patients with unclear genetic results, as management recommendations may be modified over time as research emerges. Additionally, standards and training must be developed for clinicians to become providers who can properly deliver comprehensive survivorship care.

Conclusion

Cancer risks among patients with LS are significantly elevated in comparison to the general population. Genetic screening enables identification of those who are at high risk and would benefit from more intensive preventive care. But ambiguity in PMS2 genetic test results may be seen, especially with the practice of universal tumor testing of all LS-associated cancers. With the rapid expansion of the field of cancer genetics, further clarification of diagnosis and management through both new and existing research can have significant clinical impact. Appropriately deescalating screening recommendations benefits both the medical system and the individual patient by decreasing economic and psychosocial costs. Expanding the practice of cancer survivorship to provide more comprehensive care for these patients involves incorporation of evolving clinical cancer risk management guidelines into practice. Equipping providers with the skills to care for these patients is crucial for appropriate long-term cancer prevention in the setting of hereditary cancer syndromes.

Conflicts of Interest

The authors have no conflicts of interest to disclose. This work has no external supports to disclose.

References

1. Møller P et al., "Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: First report from the prospective Lynch syndrome database". 2015;66:464-472.
2. Lynch HT and A. de la Chapelle, "Hereditary colorectal cancer". N. Engl. J. Med. 2003;348(10):919-932.
3. Broeke SW et al., "Cancer Risks for PMS2-associated Lynch Syndrome". J. Clin. Oncol. 2018;36(29)2961-2968.
4. Bartley AN, Luthra R, Saraiya SD, Urbauer DL, and Broaddus RR. "Identification of cancer patients with lynch syndrome: Clinically significant discordances and problems in tissue-based mismatch repair testing." Cancer Prev. Res. 2012;5(2):320-327.
5. Wolf AI, Buchanan AH, and Farkas LM. "Coloproctology Review article Historical review of Lynch syndrome". 2013;33(2):95-110.
6. E. O'Leary, S. Michalski, K. Ouyang, M. Kennemer, T. Ekstein, and M. Anderson, "PMS2 Pseudogene and Disambiguation: Technically Challenging, Clinically Critical," Am. J. Gastroenterol., 2014.
7. "National Comprehensive Cancer Network. Genetic / Familial High-Risk Assessment : Colorectal v 1.2016."
8. "National Comprehensive Cancer Network. Genetic / Familial High-Risk Assessment : Colorectal v 3.2019," 2019.