ACG CASE REPORTS JOURNAL

CASE REPORT | COLON

A Family With Multiple Lynch Syndrome Mutations: Navigating Counseling Complexities

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ABSTRACT

Families with multiple Lynch syndrome pathogenic variants present unique challenges in genetic counseling and clinical management. We report a family with pathogenic variants in multiple mismatch repair genes identified through multigene panel testing. Key issues highlighted by this case include recognizing when comprehensive genetic testing is necessary, tailoring management to specific genetic mutations, and ensuring accurate communication. This case highlights potential pitfalls in risk assessment and counseling for complex Lynch syndrome families.

KEYWORDS: lynch syndrome; genetic testing; genetic counseling

INTRODUCTION

The use of genetic testing is rapidly expanding beyond specialist genetics clinics.[1] Gastroenterologists navigating the complex landscape of genetic testing may be confronted with intricate cases of hereditary cancer syndromes.

Lynch syndrome, affecting approximately 1 in 279 individuals,[2] is the most common hereditary colorectal cancer syndrome and is caused by pathogenic variants in mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or deletions in the EPCAM gene. While families with Lynch syndrome typically carry a single pathogenic variant, cases involving multiple mutations can occur through various mechanisms, including partnering of mutation carriers and inheritance patterns in blended families, as illustrated in this case. These scenarios pose unique challenges for risk assessment, genetic counseling, and management recommendations.

CASE REPORT

A 60-year-old woman presented to our Gastrointestinal Cancer Genetics clinic with a history of ascending colon cancer diagnosed at the age of 52 years. Pathology revealed an invasive mucinous adenocarcinoma, and immunohistochemical analysis of the tumor showed loss of MLH1 and PMS2 protein expression. She underwent right hemicolectomy. Her family history was significant for lung cancer in her father at the age of 52 years, colon cancer in a paternal aunt at the age of 60 years, tongue cancer in a paternal uncle at the age of 75 years, endometrial cancer in her mother at the age of 48 years, and brain cancer in a maternal uncle at the age of 45 years (Figure 1). Given her personal history, family history, and tumor testing results, multigene panel testing was performed, revealing a PMS2 pathogenic variant (c.1882C>T; p.Arg628Ter).

The proband's maternal half sister was initially denied a 5-gene Lynch syndrome panel by her insurance as they stated that they would only cover testing for the familial PMS2 pathogenic variant. However, this was successfully appealed based on the fact that there was unexplained family history of cancer since her mother with endometrial cancer never underwent genetic testing. The half sister was found not to carry the familial PMS2 pathogenic variant but rather was found to carry an MSH2 pathogenic variant (c.1076+1G>A).

The proband's husband, diagnosed with colon cancer at the age of 51 years and urothelial carcinoma at the age of 57 years, carries a different MSH2 pathogenic variant (c.2458+1G>A). His family history includes pancreatic and colon cancers in his father and paternal uncle, and breast cancer in his mother.

ACG Case Rep J 2025;12:e01606. doi:10.14309/crj.0000000000001606. Published online: February 7, 2025

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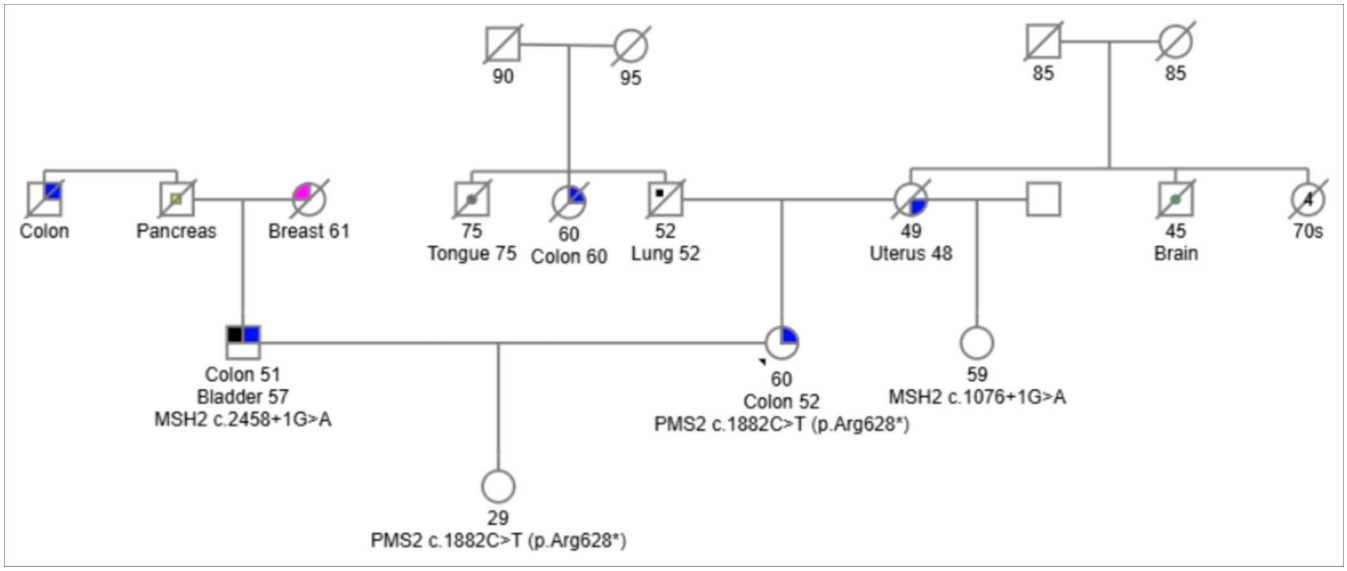

Figure 1. Pedigree of family with multiple Lynch syndrome mutations.

Their daughter inherited only the maternal PMS2 pathogenic variant. Before being seen in our clinic, the daughter received care at another practice where she received more frequent screenings than current National Comprehensive Cancer Network (NCCN) guidelines recommend for PMS2 mutation carriers of her age. She continues to request more intensive screening.

DISCUSSION

This case highlights several critical challenges that gastroenterologists may face when managing families with Lynch syndrome. These include recognizing the substantial differences in cancer risk among different mutations, ensuring appropriate genetic testing in complex families, and helping families with multiple mutations understand their risks. Addressing these challenges will become increasingly important as genetic testing becomes more common in gastroenterology practices.

Understanding mutation-specific cancer risks is crucial for appropriate patient management. MSH2 mutation carriers have a significantly higher lifetime risk of colorectal cancer (up to 52%) compared with PMS2 mutation carriers (up to 20%), leading to different NCCN screening recommendations: MSH2 mutation carriers begin colonoscopy screening at the age of 20-25 years with 1–2 year intervals, while PMS2 mutation carriers start at the age of 30–35 years with 1–3 year intervals. Regarding extracolonic gastrointestinal cancers, while current NCCN guidelines recommend the same upper endoscopic surveillance for MSH2 and PMS2 mutation carriers, their risks vary substantially: MSH2 mutation carriers face higher risks of small bowel cancer (up to 10%) and gastric cancer (up to 9%), while these risks are minimal in PMS2 mutation carriers. Endometrial cancer risk also differs markedly between MSH2 (up to 57%) and PMS2 mutation carriers (up to 26%), and unlike MSH2 mutation carriers who have up to a 38% lifetime risk of ovarian cancer, PMS2 mutation carriers appear to have no significantly elevated ovarian cancer risk. Consequently, hysterectomy with bilateral salpingo-oophorectomy is a more important consideration for MSH2 mutation carriers compared with PMS2 mutation carriers.[3]

This case demonstrates how single-gene testing could have missed clinically significant mutations, potentially leading to inadequate risk management, as illustrated by our proband's half sister who would have missed detection of her MSH2 pathogenic variant if she was tested only for the familial PMS2 pathogenic variant. Therefore, gastroenterologists should advocate for comprehensive genetic testing when family history includes unexplained cancers, particularly in complex families with multiple cancer diagnoses.

Once genetic testing has been completed and a Lynch syndrome diagnosis has been confirmed, another challenge emerges: Historically, adherence to Lynch syndrome screening guidelines has been suboptimal among both patients and clinicians, with studies showing that only 30%–70% of patients follow recommended surveillance guidelines.[4,5] In families where multiple mutations have been identified, ensuring appropriate mutation-specific risk management can become even more challenging. Patients may have inaccurate information about their own and their relatives' genetic status. To ensure accurate counseling, clinicians should obtain genetic test reports for all tested relatives and, when possible, see family members together to improve intrafamilial risk communication. Even if patients have received thorough counseling, there is a risk that patients will misunderstand their cancer risk when their family history includes multiple cancers resulting from different genetic etiologies. As demonstrated by the proband's daughter, overestimating one's risk can lead to requests for more intensive screening than guidelines recommend. Gastroenterologists

should be prepared to address such concerns while providing evidence-based recommendations.

In summary, this case illustrates the complexity of managing families with multiple Lynch syndrome mutations, where different mutations confer distinct cancer risks requiring tailored screening approaches. The growing integration of genetic testing into gastroenterology practice necessitates systematic approaches to ensure appropriate testing, accurate risk assessment, and clear intrafamilial communication. Close collaboration between gastroenterologists and genetic specialists will become increasingly vital as we continue to identify more families with multiple Lynch syndrome mutations.

DISCLOSURES

Author contributions: R Silva-Smith collected clinical data and drafted the manuscript. G Manso collected clinical data, contributed to the discussion section, and critically reviewed the manuscript. DA Sussman identified the case, collected clinical data, provided senior oversight, and critically reviewed the manuscript. All authors had full access to the relevant case information and participated in the decision to submit the manuscript for publication. Each author has reviewed and approved the final version of the manuscript. R Silva-Smith is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received September 24, 2024; Accepted January 2, 2025

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