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Case Report

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Coalescing Molecular Testing and Clinical Insights in MSH2 Positive Lynch Syndrome with Complete Immunotherapy Response

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Abstract

Lynch Syndrome, genetic predisposition syndrome is a hereditary cause of defective microsatellite instability (MSH2, MLH1, MSH6, PMS2, EPCAM) with an increased life time risk of malignancies in different organs. Prostate cancer has an accumulate risk of diagnosis in 12.8% of cases, with MSH2 and MSH6 being strongly associated with early-onset, aggressive forms. Immunotherapy has emerged as a promising treatment for patients with Lynch syndrome, particularly those with Microsatellite Instability-High (MSI-H) tumors.

This case represents the success of immunotherapy in a 69-year-old male diagnosed with MSH2 positive Lynch Syndrome and a rare presentation of prostate cancer and colorectal cancer. The next generation Sequencing preformed on tissue biopsy from recurrent metastatic adenocarcinoma involving the left lung from prostate guided the precision Oncology treatment options.

Keywords: Lynch syndrome; Prostate cancer; MSH2; Immunotherapy.

Introduction

Lynch syndrome or Hereditary Nonpolyposis Colorectal Cancer (HNPCC) is a type of inherited cancer syndrome with a genetic predisposition to different types of cancer. Lynch syndrome pathogenic alleles are widely present in humans at a 1:320 population frequency of a single allele and associated with an up to 80% risk of developing microsatellite unstable cancer (microsatellite instability – high, or MSI-H) [2]. HNPCC is inherited in an Autosomal dominant manner and is characterized by an increased risk for Colorectal Cancer (CRC) and cancers of the endometrium, ovary, stomach, small bowel, urinary tract, biliary tract, brain (usually glioblastoma), skin (sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas), pancreas, and prostate [1]. Advanced MSI-H tumors can be effectively treated with Immune Checkpoint Inhibitors (ICI) [3]. The risk prediction of prostate cancer in MSH2 gene is 3.9-23.8% [4]. Somatic and germline next-generation sequencing identified a pathogenic MSH2 mutation, consistent with a familial predisposition to Lynch syndrome.

Case presentation

A 69 years old male, with a known case of carcinoma prostate in 2013 & carcinoma colon in 2021. The patient underwent Radical Prostatectomy in 2014, and was continued on Bicalutamide and Pamorelin hormonal therapy. Exploratory Laparotomy and Right Hemicolectomy on 2021 and the patient reported metastatic Adenocarcinoma from Colon to lymph nodes. The patient 6 cycles of FOLFOX chemotherapy regimen in 2021.

PET-CT on February 2022 (Prostate surface membrane antigen expressed focal skeletal/sclerotic lesion involving L-2 vertebra, pleural plaque in lower lobe of left lung. The patient was started on Abiraterone and Prednisone with surgical Bilateral Orchiectomy was done. Subsequent PET-CT demonstrated increased pros-

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tate-specific membrane antigen expression with progression in the size and number of nodules in the left lower lobe of the lung, consistent with metastatic disease. Increase in prostate specific membrane antigen expression of sclerotic lesion involving the body of L2 vertebra. The hormonal treatment was changed to Enzalutamide + Pamorelin and then consequently to Docetaxel and Prednisone.

The biopsy of the left lung was reported to be metastatic adenocarcinoma consistent with origin from a known primary in the prostate. The immunohistochemistry report stated that the tumor cells express NKX3.1 diffusely and strongly and are negative for CK7, CK20, TTF-1 and CDX2.

Microsatellite instability testing by fragment analysis showed instability in all five markers using the Promega MSI Analysis System. Somatic tissue based next-generation sequencing was performed using a 53-gene panel to evaluate Single-Nucleotide Variants (SNVs), short insertions/deletions, Copy Number Variations (CNVs), gene fusions, and splice-site alterations. This analysis identified two Tier I variants in the MSH2 gene: a truncating variant c.778G>T (p.Glu260Ter) and an intronic splice-site variant c.2459-12A>G. The c.778G>T (p.Glu260Ter) variant was classified as Variant of Uncertain Significance (VUS), whereas the c.2459-12A>G splice-site variant was classified as likely pathogenic. Notably, both variants were detected in somatic as well as germline analyses, supporting a constitutional inactivation of MSH2.

Given the patient's personal history of cancer and a family history of colorectal and endometrial cancers, a hereditary predisposition to Lynch syndrome was suspected, and the patient was counseled to undergo germline testing. The results confirmed the diagnosis of Lynch syndrome or Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC). This integrated molecular and clinical assessment highlights the importance of combined somatic and germline profiling in accurately identifying hereditary cancer syndromes.

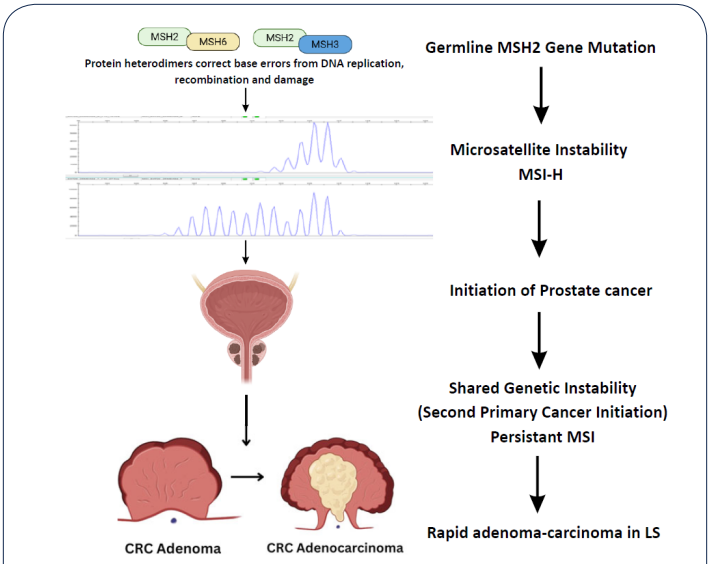

Figure 1: Schematic representation of the role of MSH2 gene mutation in Lynch Syndrome (LS)-associated tumorigenesis. Germline MSH2 mutation leads to Microsatellite Instability (MSI-H), initiating prostate cancer and promoting genetic instability, resulting in rapid colorectal adenoma-to-carcinoma progression.

Based on the MSI-H, the patient was put on Pembrolizumab Immunotherapy (30 cycles) and showed a complete resolution of the lung and bone lesions. The patient has been disease free for 1 year.

Methodology

Tissue biopsy

Sample preparation and library construction: DNA isolated from Formalin-Fixed, Paraffin-Embedded (FFPE) or other fresh tumor tissue sources was used for targeted gene capture using a custom capture kit. [5].

Microsatellite status determination by PCR

Mononucleotide repeat microsatellite sequences are particularly sensitive to transcription errors, making them ideal targets for measurement by PCR amplification. To detect MSI, fluorescently labeled primers were used to amplify the target regions from the tumor and were compared with normal reference samples. The amplified fragments were subjected to capillary electrophoresis, resulting in separation of the fragments based on their size and charge. Subsequent fluorescent labelling allowed the identification of different markers. Change in sizes indicated that there is microsatellite instability, and tumors that contain this microsatellite instability are referred to MSI-high or MSI-H. The test typically used a panel of five mononucleotide markers (e.g., BAT25, BAT26, NR21, NR24, NR27). For interpretation purposes, microsatellite instability in ≥2 loci were defined as MSI-high [6].

Genetic testing methodology

Mutation analysis was performed using semiconductor-based Next Generation Sequencing (NGS) technology. High-quality genomic DNA was subjected to target enrichment via high-multiplex PCR using the Ion AmpliSeq panel targeting mutations in the specified genes. The enriched DNA was ligated with platform-specific adaptor molecules and sequenced using a semiconductor chip. The panel achieved a minimum average depth of coverage of 500× across the targeted genes [7]. Somatic mutations were categorized into two tiers based on their clinical relevance to cancer diagnosis, prognosis, or therapeutic potential, in accordance with established international guidelines from AMP, CAP, NCCN, and ESMO [10].

Bioinformatics analysis and variant interpretation

Sequencing reads were mapped to the GRCh37/hg19 human reference, and variant calling was restricted to non-synonymous and splice-site changes within a curated gene panel, with silent (synonymous) variants excluded. Identified variants were annotated using ClinVar, COSMIC, and dbSNP; population filtering employed allele frequencies from 1000 Genomes, ExAC, dbSNP, and gnomAD. In absence of known pathogenic variants, computational predictors such as CADD, SIFT, PolyPhen-2, Condel, and MutationTaster were used to infer deleteriousness and prioritized based on patient phenotype. Final variant classification followed ACMG/AMP guidelines [8]. Library sequencing was performed on an Illumina instrument targeting >250× mean coverage depth, with quality control ensuring ≥75 % of bases met Q30 (99.9 % accuracy) or better [9].

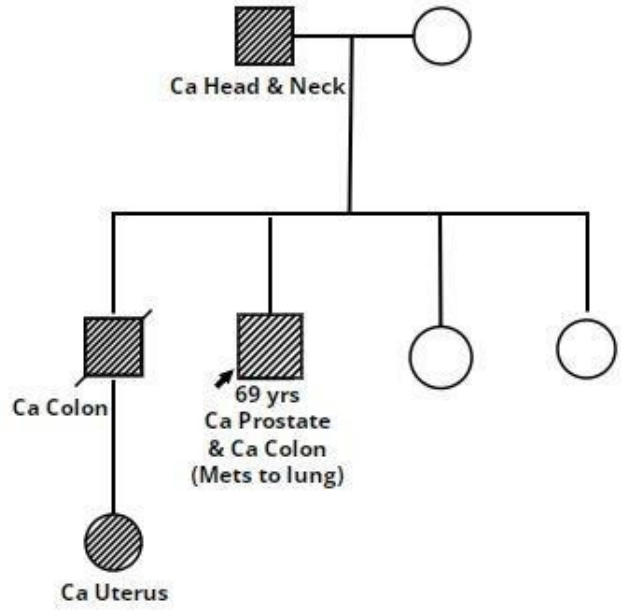

Figure 2: Pedigree illustrating a Lynch syndrome–associated cancer spectrum. The proband (indicated by an arrow) was diagnosed at 69 years with both colorectal and prostate cancer with pulmonary metastasis. A strong family history of Lynch-associated malignancies is noted, including colorectal, uterine, and head and neck cancers across two generations.

Discussion

Lynch syndrome represents one of the most common hereditary cancer predisposition syndromes. While it is classically associated with elevated risks of colorectal and endometrial cancers, affected individuals are also predisposed to a broad spectrum of malignancies, including ovarian, gastric, urinary tract (renal pelvis, ureter, bladder, and prostate), pancreaticobiliary, small intestinal, and brain tumors, as well as sebaceous neoplasms of the skin. A modestly increased risk for breast and prostate cancers has also been reported. Lynch syndrome results from pathogenic germline variants in one of the DNA Mismatch Repair (MMR) genes- MLH1, MSH2, MSH6, or PMS2 and, less commonly, from deletions in EPCAM, which cause epigenetic silencing of MSH2 [1].

Diagnosis of Lynch syndrome generally follows two principal approaches:

1. Tumor-based screening, which evaluates colorectal or endometrial cancer specimens for evidence of MMR deficiency (MMR-D) or microsatellite instability–high (MSI-H) status to identify patients warranting germline testing; and
2. Direct germline analysis in individuals whose personal or family history is suggestive of the syndrome [1].

The revised Bethesda Guidelines (2004) recommend MSI testing in colorectal cancers diagnosed before 50 years of age, tumors with mucinous, poorly differentiated, or medullary histology, and those with family histories of Lynch-associated malignancies [14]. These criteria enhance the sensitivity of detection beyond strict pedigree-based criteria and continue to guide molecular testing and genetic evaluation strategies. Molecular diagnostics now play an increasingly central role in the identification and management of Lynch syndrome, given their prognostic, therapeutic, and familial implications [13].

Among male carriers, prostate cancer risk varies by gene. By age 75 years, the cumulative incidence is reported to be 23.8% for MSH2, 13.8% for MLH1, 8.9% for MSH6, and 4.6% for PMS2 variants [11]. The IMPACT study further demonstrated the potential benefit of targeted Prostate-Specific Antigen (PSA) screening in this population: prostate cancer was more frequently detected among MSH2 (4.3%) and MSH6 (3%) carriers compared to non-carriers (0.5% and 0%, respectively) using a PSA threshold of >3.0 ng/ml. The positive predictive value of biopsy at this threshold was 51.4% (95% CI, 34–68.6%) [12].

Genetic counselling for this patient included detailed discussion of individualized preventive strategies aligned with NCCN guidelines, including upper gastrointestinal surveillance (esophagogastroduodenoscopy with duodenal evaluation) every 2-4 years for gastric cancer screening, periodic urinalysis to detect urothelial malignancies at an early stage, and vigilance for neurological symptoms suggestive of primary brain tumors [15].

From an immunological standpoint, dMMR–MSI-H tumors differ markedly from pMMR–MSS tumors. In dMMR–MSI-H cancers, defective mismatch repair results in an accumulation of mutations and generation of numerous neoantigens, which are recognized by the immune system. These tumors exhibit elevated expression of MHC class I molecules and PD-L1, accompanied by dense infiltration of $CD4^+$ and $CD8^+$ T cells and macrophages, creating a highly immunogenic tumor microenvironment. Consequently, dMMR–MSI-H tumors demonstrate strong responsiveness to immune checkpoint blockade, particularly PD-1 inhibitors such as pembrolizumab. In contrast, pMMR–MSS tumors, characterized by fewer mutations and limited neoantigen formation, exhibit a “cold” immune microenvironment with reduced T-cell infiltration and minimal responsiveness to immunotherapy. Notably, PD-1 blockade therapy with pembrolizumab has been shown to yield significantly longer progression-free survival and fewer treatment-related adverse events compared with conventional chemotherapy in patients with MSI-H/dMMR metastatic colorectal cancer.

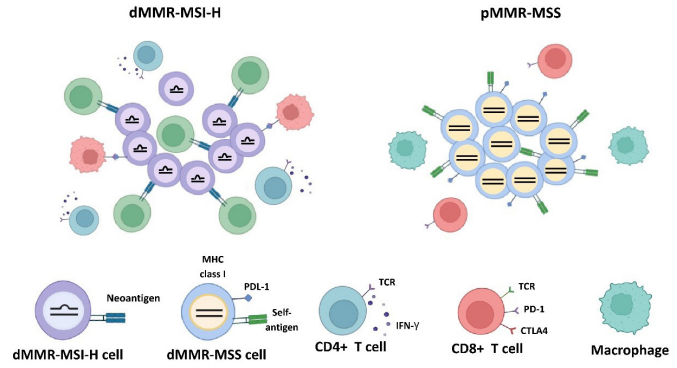

Figure 3: Comparison of tumor immune microenvironments in dMMR-MSI-H and pMMR-MSS tumors. dMMR-MSI-H tumors exhibit high neoantigen load, increased $CD4^+/CD8^+$ T cell infiltration, and enhanced immune activation. In contrast, pMMR-MSS tumors show limited T cell infiltration and immune evasion via PD-L1 expression and self-antigen presentation.

Recent advances in immunotherapy for Lynch syndrome have also focused on vaccine-based strategies and checkpoint inhibition. A Phase II trial combining a trivalent adenovirus vaccine (TriAd5) with the IL-15 superagonist N-803 (NCT05419011) aims to enhance immune activation to prevent or delay malignancy development in Lynch syndrome carriers [16]. Furthermore, multiple KEYNOTE trials have confirmed durable responses to pembrolizumab in MMR-deficient and MSI-H tumors [17]. These findings highlight the expanding role of immunotherapy both in treatment and potential prevention of Lynch syndrome-associated malignancies, underscoring the importance of continued translational research in this domain.

This case exemplifies the principles of precision oncology, where management was guided by the patient's unique genetic and molecular tumor profile, influencing decisions regarding chemotherapy, hormonal therapy, targeted agents, and immunotherapy. Our patient showed complete resolution of the bone, lung and lymph node lesions.

Conclusion

This case highlights the clinical significance of integrating somatic and germline molecular profiling in the management of malignancies associated with Lynch syndrome. The identification of a pathogenic germline MSH2 mutation and Microsatellite Instability–High (MSI-H) status was pivotal in guiding precision oncology–based treatment decisions for this patient. Despite progression on multiple lines of hormonal and chemotherapeutic regimens, the patient exhibited a complete and durable response to pembrolizumab immunotherapy, emphasizing the efficacy of immune checkpoint inhibitors in dMMR/MSI-H prostate cancer, a relatively rare manifestation of Lynch syndrome.

The case reinforces the importance of considering Lynch syndrome in patients with early-onset, aggressive, or treatment-resistant prostate cancer, particularly when accompanied by a personal or family history of other Lynch-associated malignancies. Early recognition allows not only for individualized therapeutic strategies but also for targeted surveillance and cascade testing of at-risk relatives, ultimately improving outcomes through prevention and early detection.

In conclusion, this case demonstrates how comprehensive molecular diagnostics can transform patient outcomes by enabling precision-guided immunotherapy in hereditary cancer syndromes. It underscores the expanding role of immune checkpoint inhibition as a cornerstone therapy for MSI-H/dMMR tumors beyond colorectal cancer, offering hope for long-term remission and improved quality of life in affected individuals.

Declaration of interest: The authors hereby declare that there are no conflicts of interest related to this case report. No financial, personal, or professional relationships influenced the preparation or publication of this manuscript. No funding was received for this work.

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