Case series - Mismatch repair-deficient prostate cancer: Experiences from a Canadian healthcare center

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INTRODUCTION

KEY MESSAGES

- Patients with prostate cancer (PC) harboring mismatch repair deficiency (MMRd) typically have a more aggressive disease course
- Immunotherapy is now a treatment option for patients with MMRd PC who have no satisfactory alternative treatments available
- In Canada, routine screening for MMRd in cases of high risk and metastatic PC should become widely incorporated into existing diagnostic workflows

Despite ongoing advancements, prostate cancer (PC) remains a leading cause of cancer mortality in males. Immunotherapy has revolutionized the treatment of various cancers, yet its role in treating metastatic PC has been historically ill-defined. There is now a considerable body of work demonstrating the efficacy of immunotherapy in the treatment of molecularly selected PC patients. Specifically, patients with PC harboring mismatch repair deficiency (MMRd) have been shown to benefit from immunotherapy.[1]

MMRd, an important predictor of response to immune checkpoint inhibitors in many types of cancer, is present in 3-5% of metastatic castration-resistant PC.[2,3] An accumulation of mismatch errors in DNA manifests as microsatellite instability (MSI), which can be detected even when relatively few microsatellites are included in a target DNA sequence; such is the case for targeted next generation sequencing (NGS) panels performed for detection of *BRCA1/2* mutations in PC, as the *BRCA1/2* genes each contain multiple microsatellites.[4] The increased neoantigen load in MMRd is associated with increased immunogenicity and susceptibility to immunotherapy (**Figure 1**). This is particularly significant in PC, which is typically considered

to be 'immune cold', in keeping with the low objective response rate (~5%) to immunotherapy such as pembrolizumab in unselected metastatic PC patients.[5] In contrast, objective response rates of up to 46% have been observed in MMRd PC, with 3 year progression-free survival (PFS) of up to 26%.[6–8]

In Canada, as of 2025, MMR testing for PC has only been incorporated into routine diagnostic workflow in some large academic laboratories. As with any novel biomarker-driven treatment, there exists the potential for translational gaps between urologists, pathologists, and oncologists who collaboratively order and manage biomarker testing in PC. These gaps can result in missed opportunities to identify and treat appropriate patients with pembrolizumab, which since September 2024 is Health Canada-approved for all MMRd cancers when no satisfactory alternative treatment is available. Here, we present a Canadian-perspective, single-center case series of MMRd PC, highlighting its clinicopathologic features and emphasizing the importance of identifying and managing these patients promptly.

CASE SERIES

From Feb 1, 2023 to July 1, 2025, 10 men with MMRd PC were identified during routine clinicopathologic workup at our region's central hospital (Table 1). The cases were all detected incidentally during *BRCA1/2* clinical NGS (Ampliseq for Illumina BRCA panel), which is performed at our institution on request for metastatic castration-sensitive and -resistant PC. MSI manifested in a minority of cases as small insertions and deletions in microsatellites within *BRCA1/2*. This NGS panel was not designed or validated for MSI detection, with this "off-target" application representing an informal screening method. During this period, our laboratory was not performing routine MMR testing on PC, so the true incidence of MMRd PC at our site remains unknown. Nine patients were diagnosed and managed at our center, with the remaining patient having had their tissue sent to our laboratory for biomarker testing from a community site. For all 10 cases, MMR immunohistochemistry (IHC) was performed (MLH1, PMS2, MSH2, MSH6), confirming MMR-deficiency.

The median age at diagnosis was 74 years (range 53-88 years). Median serum prostate-specific antigen (PSA) at time of diagnosis was 12 ng/mL (range 1-498 ng/mL). 50% of patients (n=5) had clinical metastatic disease at the time of diagnosis (pathologically confirmed in one patient). The remaining patients presented with locally advanced disease (≥cT3a) except a single patient who presented with cT2 disease. All cases were Gleason grade group 4 or 5. Eight patients showed MSH2/MSH6 loss on IHC (Figure 2), with the remaining showing MSH6 (n=1) and MLH1/PMS2 loss (n=1).

All patients received androgen deprivation therapy (ADT). Two patients were treated with surgery and four were treated with curative-intent radiation. All patients except one eventually progressed to metastatic disease, and routine workup revealed pathogenic *BRCA1* (n = 1) and *BRCA2* (n = 1) mutations in 2 patients, neither of whom received PARP inhibitor treatment. Of note, both mutations were frameshifts in microsatellites, i.e. most likely resulting from MMRd, and neither appeared biallelic, i.e. the mutations were present in only one allele,

leaving homologous recombination repair predominantly intact. One patient received immunotherapy following the discovery of MMRd status; this treatment was initiated following the development of peritoneal carcinomatosis. After a follow-up time of seven months since starting pembrolizumab, this patient has exhibited an excellent clinical, radiological (marked improvement in peritoneal nodularity within abdomen and pelvis on CT), and biochemical response (PSA decreased from ~100 ug/L at baseline to undetectable), with no significant adverse reactions reported. Of the 10 patients in our series, nearly half (n=4) are deceased from PC.

None of the patients had a known family history of Lynch syndrome or history of Lynch-associated malignancies. Following the finding of MMRd, 5 patients were referred to Medical Genetics, and, of the 3 tested so far, none were found to carry germline Lynch syndrome mutations.

DISCUSSION

Our case series highlights the aggressive clinicopathologic features associated with MMRd PC. Advanced stage at presentation was common, and the Gleason grade was universally high, in keeping with previous reports.[9,10] Furthermore, nearly half of the 10 MMRd PC patients included have now succumbed to their disease. Our series also demonstrates the potential for immunotherapy benefit, as observed in a patient who had developed peritoneal carcinomatosis. This patient continues to exhibit an excellent response 7 months following initiation of pembrolizumab.

MMR testing is relatively simple to incorporate into existing diagnostic workflows. MMR IHC is readily available, cost-effective, and typically straightforward to interpret.[11] Additionally, medical laboratories are increasingly using larger (500+ gene) NGS panels rather than the smaller targeted panel used historically at our institution for identifying *BRCA1/2* mutations, which have the advantage of robust built-in MSI assessment. However, a finding of MSI on NGS should be followed up with confirmatory IHC testing to determine the pattern of MMR loss and aid in assessment for Lynch syndrome.[7]

Lynch syndrome is associated with MMRd status regardless of cancer type or family history[12,13] and patients with Lynch syndrome are known to have a roughly two-fold higher rate of PC.[14] In one MMRd PC case series, 7/32 patients (21.9%) were found to have associated MMR germline mutations, highlighting the importance of medical genetics referral in these cases.[1,14] In our series, none of the patients referred to medical genetics and tested were found to have Lynch syndrome.

We note significant heterogeneity in the clinical presentations of patients in our series, with some presenting with slowly rising PSA, and others presenting emergently with advanced disease. Similarly, some patients achieved disease control with androgen deprivation, and others progressed rapidly. Serum PSA at time of diagnosis ranged dramatically (1-498 ng/mL), as reported in other series of MMRd PC.[1,9] There are no reliable clinicoradiographic predictors of

MMRd status in PC, thus highlighting the need for this testing, at least in metastatic cases with high-grade histology, as supported by the Canadian guidelines for genetic testing in PC.[15]

For Canadian practitioners, it is now time to widely incorporate MMR testing into routine practice for cases of high risk and metastatic PC. The prognostic and predictive value gained from this testing, in addition to serving as a screen for Lynch syndrome, will lead to immediate patient benefits.

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FIGURES AND TABLES

Figure 1. Schematic of mismatch repair-deficient (MMRd) prostate cancer pathogenesis and susceptibility to immunotherapy. MSI: microsatellite instability.

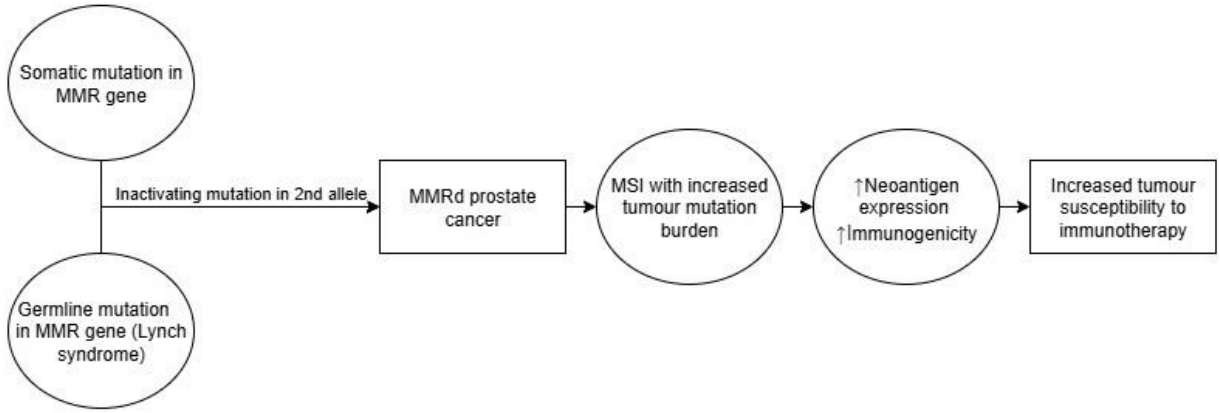

Figure 2. Photomicrographs of a representative case of mismatch repair-deficient (MMRd) prostate cancer (case #3), highlighting prostatic adenocarcinoma tumor cells with loss of MSH2/MSH6 expression and retention of MLH1/PMS2 expression on immunohistochemical evaluation (H&E: hematoxylin and eosin stain).

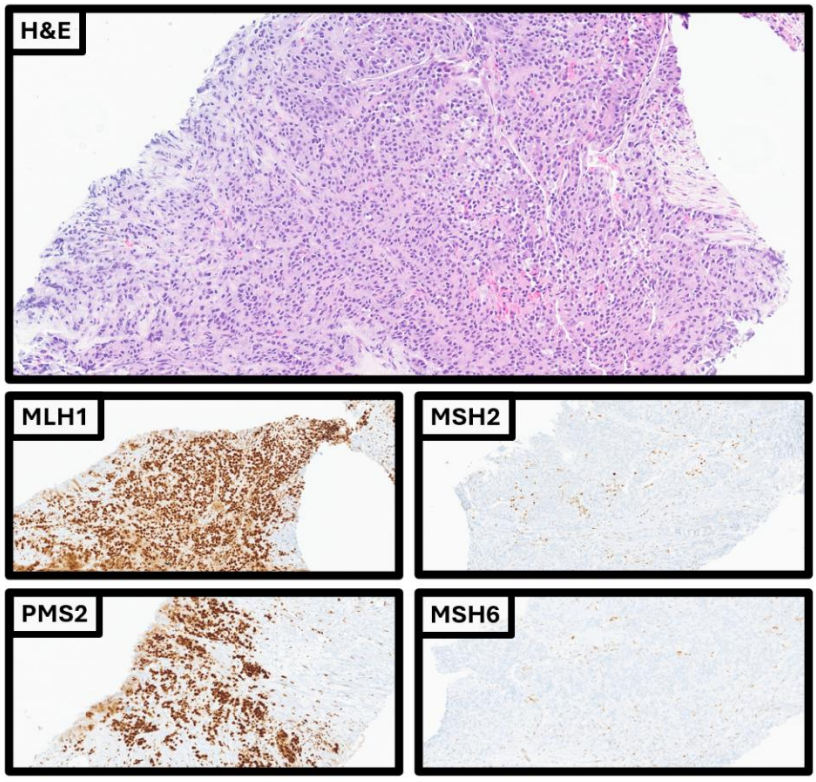

Table 1. Clinicopathologic features of mismatch repair-deficient prostate cancer

Case number	Patient age at Dx	Gleason grade group	PSA at Dx (ng/mL)	Clinical presentation	Stage at Dx	MMR protein loss on IHC	Treatment	Medical genetics followup	Most recent followup status	Months from Dx to last followup
1	68	5	6.27	Elevated PSA	pT3bN0M0	MSH2 MSH6	ADT, surgery, radiation, immunotherapy	No mutation found	PSA undetectable 07/04/2025	85
2	88	5	5.03	Prostate nodularity noted at colonoscopy	cT4N0M0	MSH2 MSH6	ADT, radiation	Not referred or tested	Deceased from PC	40 (death)
3	69	5	15.68	Elevated PSA	cT2N0M0	MSH2 MSH6	ADT, radiation	Not referred or tested	PSA undetectable 04/28/2025	36
4	80	4	62.71	Hematuria	cM1b	MSH6	ADT	Referred, no show	Deceased from PC	8 (death)
5	71	4	7.48	Elevated PSA	cT3aN0M0	MLH1 PMS2	ADT, radiation	No mutation found	Deceased from PC	36 (death)

6	81	5	229.67	Elevated PSA	cM1b	MSH2 MSH6	ADT	Not referred or tested	Deceased from PC	7 (death)
7	70	5	1.05	Urinary retention	cM1b	MSH2 MSH6	ADT	No mutation found	Deceased from other illness	14 (death)
8	76	5	10.1	Elevated PSA	cT4N0M0	MSH2 MSH6	ADT, surgery	Not referred or tested	PSA undetectable 05/02/2025	20
9	53	5	497.78	Bone metastasis	pM1b	MSH2 MSH6	ADT	Not referred or tested	PSA undetectable 07/02/2025	12
10	76	5	14.56	Elevated PSA	cM1b	MSH2/6	ADT	Not referred or tested	PSA 1.6 06/14/2025	3

ADT: androgen deprivation therapy; Dx: diagnosis; IHC: immunohistochemistry; MMR: mismatch repair; PSA: prostate specific antigen.