Survival of Mismatch Repair Deficient Endometrial Cancer in a Black Population

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Introduction

- Endometrial cancer (EC) poses a significant health burden, particularly affecting minority women, among whom Black women are disproportionately impacted. Nearly one-third of these individuals exhibit abnormalities in the DNA Mismatch Repair (MMR) pathway. These abnormalities involve deficiencies in crucial MMR proteins, namely MSH2, MLH1, PMS1, and PMS2, identified through immunochemistry.
- MMR deficiency can bring about a series of impactful physiological events through the accumulating DNA base pair mismatches and genomic alterations. A detrimental consequence of these alterations is the unregulated cellular growth and the development of invasive cancers.
- The origin of MMR deficiency can be traced to hereditary loss, as seen in Lynch syndrome, or acquired through sporadic means, most notably via epigenomic hypermethylation of the MLH1 gene.
- Despite the significance of these findings, the impact of mismatch repair deficiency (MMRd) and its role within the minority EC population remains insufficiently explored. Therefore, the primary objective of this study was to investigate the prognostic implications of hereditary or sporadically acquired MMRd concerning presentation and survival within the minority EC population in southwest Louisiana.

Methods

- We carried out a retrospective cohort study encompassing minority patients diagnosed with endometrial cancer (EC) who underwent MMR (DNA Mismatch Repair) testing and received medical care from LSUHSC-associated gynecologic oncologists between 2018 and 2023.
- Comprehensive chart review was performed to extract patient demographic, clinicopathologic, and survival data. Collected data was entered and stored into a REDCap database.
- To gain insights into the dataset, we employed statistical analyses, comprising summary statistics and pairwise comparisons.
- Our objective was to ascertain whether significant variations existed in terms of cancer stage, grade, and histology at presentation, based on the mode of MMRd acquisition among minority EC patients.

Figure 1: MMR Deficiency Prevalences

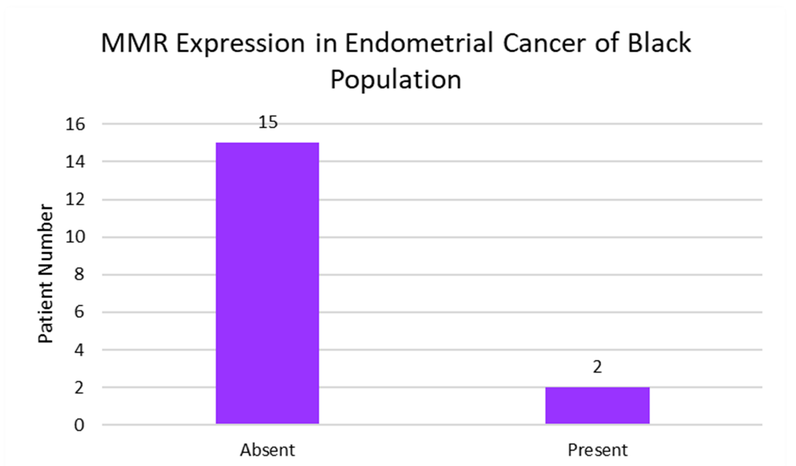

Figure 1: Among the Black EC patients in southwest Louisiana, 8.50% (N=17) exhibited MMR deficiency (MMRd). Majority of patients, n=15 (88.2%), presented with sporadic MMRd characterized by mutation across 22 genes.

Figure 2: Prevalence of MMR Proteins

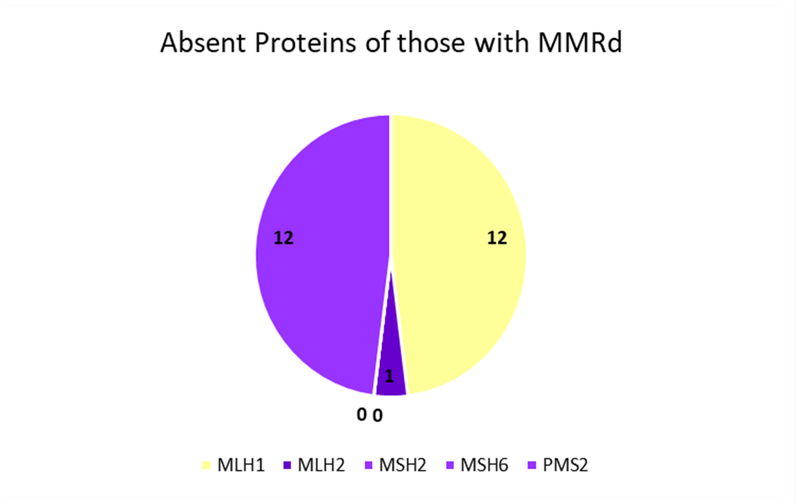

Figure 2: Several patients exhibited concurrent mutations in multiple MMR genes, such as simultaneous mutations in MLH1 and PMS2. Consequently, the most frequently affected MMR genes were PMS2 (n=12, 80.0%), MLH1 (n=12, 80.0%), and MLH2 (n=1, 6.7%). Only one patient within this cohort demonstrated hereditary MMR loss, specifically in the PMS2 gene. In situations of absent MMR function, 53.3% (n=8) presented with hypermethylation of the MLH1 promoter.

Results

- **Study Cohort:** Out of 200 patient charts reviewed for individuals identifying as Black with EC, **N=17** (8.50%) exhibited MMRd.
- **Mode of MMRd Acquisition:** The majority of patients, **n=15 (88.2%)**, presented with sporadic MMRd, characterized by mutations across **22 genes**.
- **Concurrent Mutations:** Some patients displayed concurrent mutations in multiple MMR genes, such as simultaneous mutations in **MLH1 and PMS2**. The most frequently affected MMR genes were **PMS2 (n=12, 80.0%)**, **MLH1 (n=12, 80.0%)**, and **MLH2 (n=1, 6.7%)**.
- **Hereditary MMR Loss:** Only one patient within this cohort demonstrated hereditary MMR loss, specifically in the **PMS2 gene**.
- **MMR Function Absence:** In cases where MMR function was absent, **53.3% (n=8)** of patients presented with hypermethylation of the **MLH1 promoter**.
- **Cancer Staging:** Among the 17 MMRd patients, **70.60% (n=12)** presented with **Early-Stage EC** (Stage I or II), while **29.4% (n=5)** presented with **Advanced-Stage EC** (Stage III/IV).
- **Histological Classification:** Histologically, **35.3%** of cases were classified as **Grade 1 EC (n=6)**, **29.4%** as **Grade 2 (n=5)**, **23.5%** as **Grade 3 (n=4)**, and **11.6%** were either not reported or classified as "other" (n=2).
- **Histological Subtype:** Overall, **76.5%** of our population presented with histology indicating **Endometrioid Adenocarcinoma (EAC) (n=13)**, while both **Carcinosarcoma** and **Uterine Papillary Serous Carcinoma** each accounted for **11.8%** of the cases (2 cases each).
- **Survival Outcomes:** Of the MMRd patients, **70.6% (n=12)** are currently **alive with no evidence of disease**, **11.8%** are **alive with disease (n=2)**, and **11.8%** sadly **died from cancer-related reasons (n=2)**.

Conclusion

- In conclusion, our study offers valuable insights into the clinical characteristics and outcomes of Black women with MMRd EC. In our population, Mismatch Repair Deficiency (MMRd) was identified in 8.50% of the 200 patients examined. The majority of these cases were sporadically acquired MMRd, characterized by mutations across multiple genes, with PMS2 and MLH1 being the most frequently affected MMR genes. It was also noted that hypermethylation of the MLH1 promoter was a common feature when MMR function was absent. Histologically, various grades and subtypes were observed, with Endometrioid Adenocarcinoma (EAC) being the most prevalent subtype.
- Given the limited sample size, larger-scale investigations are warranted to validate these findings and explore potential racial and ethnic disparities further. Understanding the impact of MMRd in minority populations is essential for tailoring effective treatments and improving outcomes in the fight against endometrial cancer.

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