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An update on central nervous system tumors in germline replication-repair deficiency syndromes

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Abstract

DNA replication-repair deficiency (RRD) arises from pathogenic variants in the mismatch repair and/or polymerase-proofreading genes. Multiple germline cancer predisposition syndromes in children and young adults, including constitutional mismatch repair deficiency (CMMRD), Lynch, polymerase-proofreading deficiency, and rare digenic syndromes can lead to RRD cancers. The most frequent brain tumors in these children are high-grade gliomas. Embryonal tumors like medulloblastoma have also been described. Lower-grade tumors are reported from cancer surveillance initiatives. The latter has an extremely high rate of malignant transformation. Novel functional assays quantifying the genomic microsatellite indel load have been demonstrated to be highly sensitive and specific for the diagnosis of RRD cancers and children with germline CMMRD. Importantly, RRD brain tumors uniformly harbor high mutation and microsatellite burden. High T-cell infiltration makes these aggressive cancers amenable to immune checkpoint inhibition, irrespective of their germline genetic background. Synergistic combinations are reported to be successful in patients failing checkpoint inhibitor monotherapy. Future directions include the development of innovative approaches to improve immune surveillance for RRD brain cancers. Additionally, the use of novel tools including circulating tumor DNA and quantifying microsatellite indel load over time can be useful to monitor disease burden and treatment responses in patients.

Keywords

glioblastoma | hypermutation | immunotherapy | microsatellite instability

Fidelity of DNA replication during cell division is maintained by the mismatch repair (MMR: *PMS2, MSH6, MLH1, and MSH2)* and polymerase-proofreading genes (PP: *POLE, POLD1*).[1,2] Aberrations in these genes lead to errors in the genome through the accumulation of large numbers of single nucleotide variants and insertions/deletions (indels).[3,4] The latter is frequent in repetitive DNA segments (microsatellites), leading to microsatellite instability (MSI).[5] Ultimately, MMR and/or PP deficiency (MMRD/PPD) lead to cancers with high single nucleotide variants or tumor mutation burden (TMB) and MSI, which together, constitute the hallmarks of DNA replication-repair deficiency (RRD).

While RRD is a pan-cancer mechanism, germline pathogenic variants in MMR, *POLE/POLD1*, and certain related upstream promoter genes, lead to cancer predisposition syndromes with overlapping biological characteristics.[6] Germline RRD is, therefore, an umbrella terminology for several related syndromes, including constitutional or biallelic MMR deficiency (CMMRD), heterozygous Lynch syndrome (LS), patients with germline heterozygous *POLE* variants and rare patients with digenic defects in MMR and *POLE* genes (Figure 1A).[7] While multiple cancer types develop in these individuals, central nervous system (CNS) and gastrointestinal cancers form the main burden of cancers in these syndromes in childhood.[8,9] In the "Think Tank" on Genetic Predisposition to Primary CNS cancers, we focus on highlighting recent advances in the biological understanding, diagnostics, and treatment of CNS cancers arising in the germline RRD syndromes.

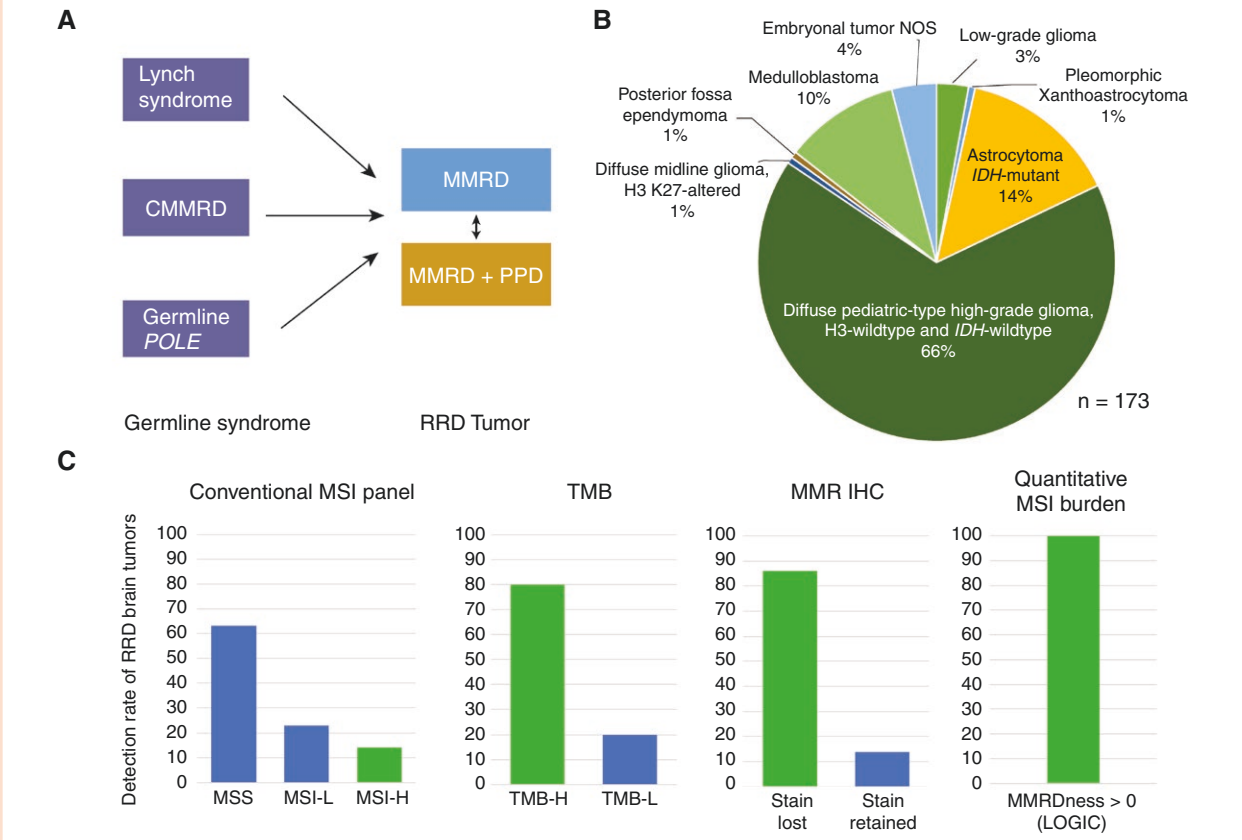

Figure 1. **(A)** Patients with germline heterozygous Lynch syndrome, constitutional mismatch repair deficiency (CMMRD), and germline heterozygous *POLE* variants can develop cancers with biallelic MMR deficiency and polymerase-proofreading deficiencies due to gain of additional somatic hits. **(B)** The expanded spectrum of central nervous system cancers in patients with CMMRD.[8] **(C)** Comparison of conventional MSI panel (Microsatellite Instability Analysis System, Promega, WI), TMB, immunohistochemistry, and LOGIC in the detection of MMR deficiency in replication-repair deficiency (RRD) brain tumors. Relative to these diagnostic tools, functional genomic assays quantifying the whole genomic MSI burden like LOGIC have superior sensitivity and specificity in diagnosing MMR deficiency in brain tumor tissues.[4,5] Abbreviations: MMRD, mismatch repair deficiency; PPD, polymerase-proofreading deficiency; MSI, microsatellite indel/ instability; MSS, microsatellite stable; H, high; L, low; TMB, tumor mutation burden; IHC, Immunohistochemistry; LOGIC, low-coverage genomic instability characterization. Figures were generated using data from the International RRD Consortium.

Expanding CNS Cancer Phenotype and Genotype Associations in Germline RRD

Collaborative efforts through the International RRD Consortium (IRRDC; https://replicationrepair.ca) and other networks have revealed that CNS cancers are common across all the RRD genes and genotypes.[8] In contrast to primary glioma driver mutations in genes like *TP53* and *NF1,* which are frequently somatic and only infrequently stem from respective germline predisposition syndromes, most primary gliomas with mutations in RRD genes will stem from germline RRD. This mandates expanded evaluation for the patient and cascade testing for family members. Importantly, an expanded spectrum of tumors beyond diffuse pediatric-type high-grade glioma H3-wildtype and *IDH*-wild type (pHGG) is now well-appreciated (Figure 1B).[8,10,11] These include astrocytoma *IDH*-mutant, posterior fossa ependymoma, medulloblastoma, and other embryonal tumors, both in children and young adults.[8,11–13] Lower-grade tumors, including optic pathway gliomas, are diagnosed mainly through surveillance protocols. It is important to note that low-grade gliomas in germline RRD are uniquely prone to rapid transformation to high-grade gliomas, mandating specialized management.[9]

While CMMRD remains the most common cause for RRD CNS tumors in children, CNS tumors in LS patients are increasingly reported.[14,15] Both grade 3 astrocytoma *IDH*-mutant and pHGG are described, especially in adolescents and young adults. As these patients do not exhibit non-cancer stigmata, their diagnosis is commonly missed. This likely contributes to inferior outcomes. Likewise, germline heterozygous *POLE* patients, who were initially considered to have PP-associated polyposis (PPAP) syndrome, are now well-described to develop pHGG at young ages. Last, medulloblastoma and embryonal tumors have been diagnosed in both germline *POLE*, as well as in rare digenic patients with both LS and PPD.[6,16] It remains unclear which individuals with LS/ PPD syndromes are predisposed to develop CNS tumors at young ages rather than gastrointestinal or genitourinary malignancies. However, it is

Table 1. Characteristics of Different Genotypes in Patients With CMMRD (n = 201)[8]

Characteristics	*PMS2*	*MSH6*	*MLH1*	*MSH2*
Prevalence within CMMRD	65%	25%	6%	2.5%
Median age at diagnosis	8.9 years	9.1 years	7.7 years	4.9 years
Gender ratio (male: female)	1.2:1	0.9:1	1:2	3:2
Cancer types				
Central nervous system	49%	55%	50%	67%
Gastrointestinal	23%	16%	33%	33%
Hematological	18%	23%	6%	0
Others	10%	6%	11%	0
Estimated survival at age 15 y	50%	50%	9%	0

likely that such individuals have been previously underdiagnosed due to a lack of testing for RRD and rapid fatality from their aggressive CNS tumors.

Biologically, LS tumors acquire biallelic MMRD during carcinogenesis. Furthermore, CNS cancers from both LS and CMMRD have a high chance of acquiring somatic mutations in additional RRD genes. Specifically, a combination of MMRD and PPD can result in extreme TMB exceeding 100 mutations/megabase (ultra-hypermutation).[3] Conversely, *POLE/POLD1*-driven CNS tumors commonly develop secondary somatic MMRD. In addition, RRD CNS cancers exhibit enrichment for somatic driver mutations in genes including *TP53, ATRX*, the *RAS/MAP*-kinase pathway, and *IDH1*.[8] Additionally, while these RRD CNS tumors still have higher MSI as compared to other CNS tumors, MSI burden is lower than that observed in non-CNS RRD cancers.[4,8] These biological findings have important implications for the diagnosis and management of CNS cancers arising in RRD predisposition syndromes.

Importantly, the IRRDC has recently unearthed novel genotype-phenotype associations, specifically in individuals with CMMRD.[8] While *PMS2* and *MSH6* are commonly affected genes in CMMRD, individuals with biallelic germline *MSH2* or *MLH1* affected, and those with truncating variants across all four genes, not only have an earlier onset of cancers, including CNS tumors, but also have inferior survival, highlighting the relative biologic effects and dependencies in the MMR mechanism (Table 1).

Novel Diagnostic Tools to Detect RRD in Cancer and in the Germline

RRD cancers uniformly harbor high TMB and MSI, as well as characteristic patterns of genomic error accumulation, identifiable as specific mutational and microsatellite signatures. This allows the opportunity to use these as potential diagnostic tools. However, both TMB and immunohistochemistry for MMR protein expression, while useful, have limitations in detecting RRD in tumor samples.[4,17,18] This has supported the development of functional genomic assays that harness the characteristic high genomic MSI burden in RRD cancers.

It is important to note that traditional panel-based MSI testing is of limited benefit in germline RRD patients and specifically RRD CNS tumors, as microsatellite signatures in this context are unique and different from adult and gastrointestinal tumors for which such specific panels were developed. In contrast, several functional genomic assays quantifying the complete MSI burden have been reported to have superior diagnostic yield for RRD cancers.[5,19,20] Specifically, one such assay, termed low-coverage genomic instability characterization (LOGIC), has been reported to have excellent sensitivity and specificity to diagnose RRD in tumors in a scalable and inexpensive way (Figure 1C).[5] The low-coverage genome sequencing can additionally be used to detect specific mutations and copy number changes in the tumor. Furthermore, LOGIC is extremely sensitive to diagnose CMMRD in the germline, as due to biallelic germline MMR deficiency, these patients have relatively high MSI burden in their nonmalignant (blood and saliva) tissues.[5] Last, LOGIC was found to be useful in resolving difficult cases, allowing the correct diagnosis in patients and families in low-income settings in twinning programs by the IRRDC.[17]

Together, the use of TMB, MSI, and their unique signatures results in extremely high sensitivity and specificity in diagnosing CNS RRD cancers and tracing them to the germline. These allow for early detection of cancers through the implementation of surveillance protocols and tailoring therapy for these cancers ultimately improving outcomes for these patients.

Advances in Therapies for CNS Tumors in Germline RRD

Aggressive RRD gliomas historically had extremely poor survival (Figure 2A, B). Temozolomide, which requires an intact MMR machinery for efficacy, is not useful, although Lomustine (CCNU) is an effective agent.[21] However, the extreme TMB and MSI allow these CNS tumors to have a pro-immune or "hot" immune microenvironment with high CD8 positive T-cell infiltration and PD-L1 expression.[22] The efficacy of immune checkpoint inhibition (ICI) using PD1 blockade has therefore led to remarkable radiological responses and prolonged survival in patients with progressive/ refractory RRD high-grade gliomas (Figure 2C–E).[14,22,23] Nearly a third of patients are disease-free at 4-year follow-up on anti-PD1 treatment.[24] Additionally, several clinically

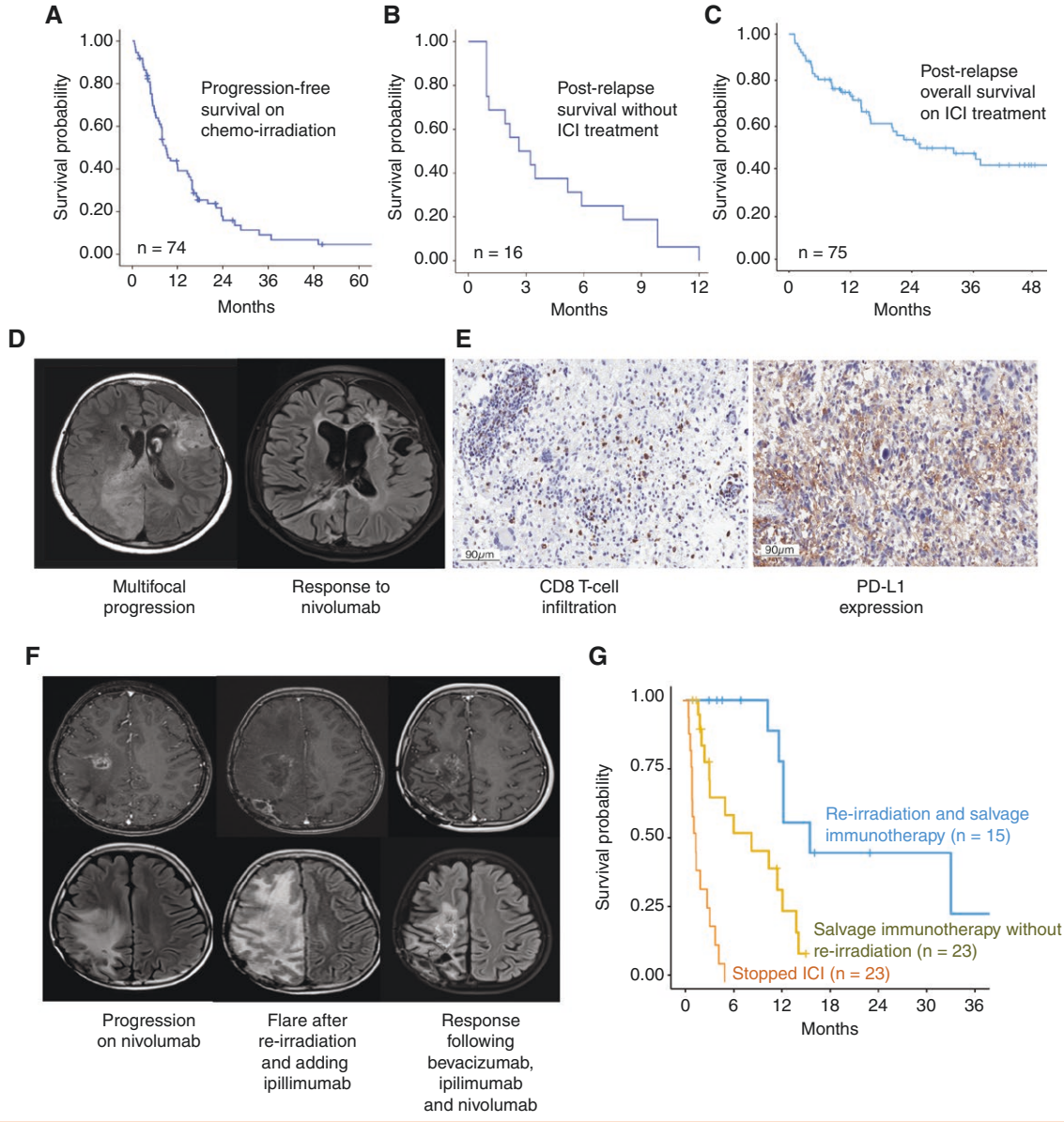

Figure 2. **(A)** Progression-free survival (median: 9 months) following chemoradiation in patients with replication-repair deficiency (RRD) high-grade glioma. **(B)** Post-relapse survival (median: 2.6 months) in patients with RRD high-grade glioma without immune checkpoint inhibition (ICI). **(C)** Overall survival (median: 25.5 months) for patients with progressive RRD high-grade glioma on ICI treatment.[14,22,23] **(D)** Complete response to nivolumab in a child with CMMRD and multifocal progressive high-grade glioma. **(E)** High CD8 T-cell infiltration and PD-L1 expression are observed in good responders to ICI.[22] **(F)** Patient with RRD high-grade glioma progressing on nivolumab was treated with re-irradiation and the addition of ipilimumab. "Flare" following combination treatment was managed using Bevacizumab in order to avoid the immunosuppressive effect of steroids. **(G)** Patients with RRD high-grade glioma progressing on anti-PD1 treatment. Continuation of immune-directed salvage therapies improved survival.[24] Those receiving re-irradiation in addition to combination treatment had the best outcomes.

relevant biological insights have been gained from these studies. Prognostic biomarkers identified include TMB, MSI, CD8, and PD-L1 expression.[22] Remarkably, high-grade glioma with a combination of these favorable biomarkers had excellent survival at relapse, prompting upfront ICI use in a select cohort of patients, allowing avoidance of radiation and chemotherapy.[25] This strategy will now be tested in an international, response-adapted clinical trial with an aim to avoid or delay radiation.

It is also important to underscore that a subset of patients, especially those with bulky disease, are at risk of "immune flare."[14] Conventional MRI sequences have limited utility in distinguishing true progression from immune flare. Perfusion-weighted MRI, use of iron nanoparticles, and positron emission tomography using radiotracers have shown early promise in identifying inflammation in specific studies but need further validation for routine clinical use.[26,27] Biopsy, albeit helpful, is not feasible in a

majority of cases, thereby generating interest in cell-free DNA and flow cytometry-based biomarker approaches to distinguish this in the future.[22,26,27] Notably, however, excellent supportive care and continuing ICI after clinical stabilization of patients with immune flare, ideally while avoiding steroids and instead using anti-VEGF (personal experience; Figure 2F) allows delayed responses and prolonged survival. Peripheral blood biomarkers for activated and proliferating T-cells and cerebrospinal fluid testing can be useful to identify such patients.[22]

Radiotherapy remains an excellent modality for treating RRD CNS cancers, as radiation per se does not increase the risk of subsequent malignancies in germline RRD. Re-irradiation was recently found to be effective in inducing objective responses in synergism with ICI treatment. This was partly related to the lack of radio-resistant genomic signatures (ID8) in RRD gliomas previously treated with radiation. It is postulated that these indels were immunogenic and hence were immune-edited following ICI therapy, leading to retained radiation sensitivity (Figure 2G).[24]

Finally, immune-directed combinatorial therapies have shown encouraging results for cancers refractory to anti-PD1 monotherapy. Genomic instability leads to continuous mutation accumulation that impacts the microenvironment and can result in delayed responses despite initial progression. Furthermore, compensatory upregulation of untreated checkpoints allows inhibitors to be directed against them. Adding ipilimumab (anti-CTLA4) after failing nivolumab (anti-PD1) was linked to higher CTLA4 expression at progression and led to prolonged survival.[24] In addition, oncogenic addiction of RRD gliomas to the *RAS/MAP*-kinase pathway that can get enriched over time, allowed targeted MEK-inhibition in combination with ICI to result in radiological responses, as well as synergism to invigorate the peripheral immune responses.[24,28] As the mutational spectrum evolves rapidly in these cancers and can impact the immune microenvironment, safe debulking at progression can allow both the identification of novel vulnerabilities, as well as reduced disease burden for effective immune-directed combinatorial strategies.[24,28] These combinatorial approaches will now be evaluated in prospective consortia clinical trials.

It is important to reiterate that all RRD CNS tumors, including germline LS and PPD, acquire similar immunogenomic characteristics as germline biallelic/CMMRD patients and can respond similarly to ICI treatment.[14] However, as the CMMRD hosts harbor higher mutations in normal cells, combinatorial ICI leads to higher systemic immune toxicities in CMMRD than LS, plausibly due to higher neoantigen load even in nonmalignant/non-target tissues.[24] These data need to be considered while developing future treatment strategies for these patients.

Future Directions

Raised awareness and novel assays have contributed to the expansion of the spectrum and impact of RRD in CNS tumors. This has allowed the diagnosis of RRD in CNS tumors, tracing of specific variants to the germline, timely implementation of surveillance, cascade testing, and use of immune therapies for these previously deadly cancers. However, several challenges remain. The risk of subsequent malignancies is high, especially in CMMRD, with patients developing new cancers every two years.[8] Improved surveillance and monitoring tools are therefore needed. Circulating tumor DNA (ctDNA) based approaches are promising and need to be further developed and validated for both surveillance in cancer-unaffected patients with CMMRD, and monitoring response to immune-directed therapies for those with cancers, given the challenges with radiological assessments highlighted above. Likewise, the optimal duration of immunotherapy and risk of immune toxicities need to be better understood and managed, and protocols for tapering treatment with radiology and ctDNA-based monitoring are being developed by the IRRDC and other interest groups. While immune surveillance is useful, escape and resistance are major concerns. Prevention or interception approaches including vaccines and combinatorial strategies can be useful and need to be systematically developed and tested. Finally, international collaboration needs to be strengthened to better understand the biology, genotype associations, and improve the outcomes for patients with these syndromes globally.[29]

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Conflict of interest statement

None.

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