Durable Response to Nivolumab in a Pediatric Patient with Refractory Glioblastoma and Constitutional Biallelic Mismatch Repair Deficiency.


Department of Oncology, Comprehensive Cancer Centre, King Fahad Medical City, Riyadh, Saudi Arabia.

Primary brain tumors are a leading cause of cancer-related morbidity and mortality in children. Glioblastoma (GBM) is a high-grade astrocytoma that occurs in both children and adults and is associated with a poor prognosis. Despite extensive study in recent years, the clinical management of these tumors has remained largely unchanged, consisting of surgical resection, conventional chemotherapy, and radiotherapy. Although the etiology and genomic drivers in GBM are diverse, constitutional mismatch repair-deficiency (CMMRD) syndrome is a rare, recessively inherited disease with a predisposition to gliomagenesis. CMMRD results from biallelic mutations in one of the mismatch repair genes including MLH1, MSH2, MSH6, and PMS2. In this report, we present the case of a 5-year-old female with GBM and CMMRD due to an MSH6 homozygous c.1883G>A mutation, who continues to experience an exceptional and durable response (9 months) to the immune checkpoint inhibitor (ICPI) nivolumab. Our patient presented with acute neurologic decline and increased intracranial pressure. Neuroimaging studies revealed a large left frontoparietal mass requiring neurosurgical decompression and resection. Histopathologic analyses resulted in a diagnosis of de novo GBM that was BRAF wild type and negative for programmed death-ligand 1 protein expression. She received standard-of-care treatment with surgery, radiation therapy, and temozolomide; however, the tumor recurred 3 months after the initial diagnosis. Molecular analyses of tumor and blood tissues revealed an MSH6 homozygous c.1883G>A mutation consistent with CMMRD. Given her CMMRD status, she was treated with nivolumab (3 mg/kg doses every 2 weeks for 36 weeks) and showed a 60% reduction in tumor size, improved clinical symptoms, and an ongoing durable response lasting 10 months to date. Our study highlights a durable response to the ICPI nivolumab in a pediatric patient with recurrent/refractory CMMRD-associated GBM. We show that incorporating genomic and/or molecular testing for CMMRD into routine pediatric oncology clinical care can identify a subset of patients likely to benefit from ICPI.

**KEY POINTS:** Constitutional mismatch repair-deficiency (CMMRD) syndrome, alternatively known as biallelic mismatch repair deficiency syndrome, occurs in subset of pediatric cancer...
patients, including those with primary brain tumors. Patients from Arab and other developing countries are predicted to have higher incidence of CMMRD due to high prevalence of consanguinity. Integration of molecular and/or genomic testing into routine clinical care for pediatric cancer patients is important to identify patients with CMMRD syndrome. Patient with CMMRD-associated cancers may show increased responsiveness to immune checkpoint inhibitors. To the authors' knowledge, this is the first report in the Arab world of a durable response to immune checkpoint inhibitors in a pediatric glioblastoma patient.


PMID: 30104292 DOI: 10.1634/theoncologist.2018-0163