

CASE REPORTS | May 23, 2024



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Dabrafenib for Pilocytic Astrocytoma With *BRAF V599ins*

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Introduction

Low-grade glioma (LGG) stands as the most prevalent type of CNS tumor in children,¹ with the *BRAF V600* mutation recognized as the second most common molecular feature in pediatric LGG. Recent studies have illuminated the challenges faced when treating *BRAF V600*-mutated LGGs using conventional chemotherapy, where they often exhibit resistance or a high relapse rate.² Notably, RAF inhibitor monotherapy, or its combination with a MEK inhibitor, has shown remarkable improvements in tumor control and progression-free survival.³⁻⁸ Although *BRAF V600E* is the most frequently occurring *BRAF V600* mutation, it is not the exclusive one.⁹⁻¹¹ Clinical diagnosis using immunohistochemistry (IHC) antibodies can accurately detect *BRAF V600E* without the need for next-generation sequencing. However, there are minor variations of *BRAF V600* that may elude detection via IHC, potentially resulting in missed therapeutic opportunities.⁹ *BRAF V599ins* has been identified in some cancers, including papillary thyroid carcinoma and melanoma.¹¹⁻¹⁶ Extensive biochemical and molecular characterization of *BRAF V599ins* has affirmed its activation and mechanism similarity to *BRAF V600E*, indicating potential responsiveness to RAF inhibitors.¹⁴ Yet, clinical documentation of RAF inhibitor utilization for patients with *BRAF V599ins* remains unreported.

Case Report

An 8-year-old boy was admitted to the hospital because of worsening ataxia, which had developed over the course of 3-4 months, accompanied by persistent headaches. He was initially evaluated by his primary pediatrician and neurologist where working diagnoses involving spinal cord and neuromuscular pathology were considered. Subsequently, he presented to the emergency room with progressively worsening ataxia while awaiting electively scheduled CNS imaging. A computed tomography scan of his head revealed significant enlargement of the lateral and third ventricles, secondary to a lesion in the midbrain and left middle cerebellar peduncle. Subsequently, he underwent an endoscopic third ventriculostomy and biopsy of the lesion. A magnetic resonance imaging (MRI) of the brain unveiled an infiltrative solid cystic mass in the left brain stem, measuring 2.2 × 3.1 × 3.8 cm (transverse, anterior-posterior, craniocaudal), exhibiting focal contrast enhancement, and a mild increase in apparent diffusion coefficient (Fig 1). Unfortunately, the endoscopic biopsy specimen proved insufficient for a definitive diagnosis. Consequently, a robot-assisted stereotaxic needle biopsy of the left cerebellar peduncle part of tumor was performed, ultimately confirming pilocytic astrocytoma with negative immunohistochemistry for *BRAF V600E* (Fig 2). However, whole-exome sequencing of the specimen revealed the presence of *BRAF c.1794_1795insGTT*, resulting in the insertion of valine between alanine at 598 and threonine at 599.

In light of the molecular features of the tumor and recent compelling data supporting molecular targeted therapy over conventional chemotherapy, treatment with the *BRAF* inhibitor dabrafenib was initiated for his pilocytic astrocytoma. We opted for monotherapy with a *BRAF* inhibitor because it is essential to assess the tumor's response to monotherapy especially with the rare mutation type. Before his treatment, he was unable to stand because of severe ataxia and developed Parinaud syndrome, exhibiting restricted upward gaze. Within a week, he began showing signs of symptom improvement, regaining the ability to walk and eventually ran with mild ataxia. His first therapy evaluation MRI, taken 3 months after the initiation of dabrafenib, showed a significant reduction in tumor size (Fig 1). To the best of our knowledge, this case marks the first clinical report of LGG with *BRAF V599ins* successfully treated with dabrafenib. Our patient has been consistently receiving dabrafenib for 5 months with minimal side effects

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