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Targeted Therapeutic Strategies and Molecular Insights in Medulloblastoma: A Case Report

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ABSTRACT

Medulloblastoma is the most common malignant pediatric brain tumor, characterized by aggressive growth, early dissemination through the cerebrospinal fluid, and a complex molecular landscape. Recent advances in genomic and transcriptomic profiling have revealed distinct molecular subgroups—WNT, SHH, Group 3, and Group 4—that influence prognosis, treatment response, and potential for targeted interventions. This report presents a case of SHH-subgroup medulloblastoma treated with a combination of surgical resection, craniospinal irradiation, and SHH-targeted therapy, highlighting the role of precision medicine in guiding therapy. The integration of molecularly guided targeted interventions alongside standard-of-care treatment demonstrates potential for improved disease control, preservation of neurocognitive function, and reduced systemic toxicity. These findings emphasize the importance of early molecular characterization to enable individualized treatment strategies in pediatric medulloblastoma.

Keywords

Medulloblastoma; SHH pathway; Targeted therapy; Pediatric brain tumor; Precision medicine; Vismodegib; Molecular profiling.

INTRODUCTION

Medulloblastoma arises primarily in the cerebellum and accounts for approximately 20% of pediatric brain tumors. Clinical presentation commonly includes headache, nausea, vomiting, ataxia, and signs of increased intracranial pressure due to obstructive hydrocephalus. Historically, management has relied on maximal safe surgical resection, craniospinal irradiation [1], and multi-agent chemotherapy. While these approaches have significantly improved overall survival, long-term complications—including neurocognitive deficits, endocrine dysfunction, and secondary malignancies—remain substantial, particularly in younger children.

In recent years, high-throughput molecular profiling has revolutionized our understanding of medulloblastoma biology. The identification of four principal molecular subgroups—WNT, SHH, Group 3, and Group 4—has enabled risk stratification, prognostication, and the development of targeted therapeutic strategies. Among these, the SHH (Sonic Hedgehog) subgroup, accounting for approximately 30% of pediatric cases, is characterized by dysregulation of the SHH signaling pathway, often involving mutations in PTCH1, SMO, or SUFU. This subgroup is amenable to pathway-specific targeted therapies, including small molecule inhibitors such as vismodegib and sonidegib [2].

Integration of targeted molecular therapy with conventional approaches offers an opportunity to maximize tumor control while minimizing systemic toxicity. However, challenges such as drug resistance, optimal timing of therapy, and long-term effects remain under investigation. This case report highlights the clinical application of precision medicine in managing an SHH-subgroup medulloblastoma, emphasizing both therapeutic efficacy and patient-centered outcomes.

A 7-year-old male presented with a three-week history of progressive headaches, nausea, and imbalance. Neurological examination revealed truncal ataxia and mild dysmetria. Magnetic resonance imaging (MRI) identified a midline

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cerebellar mass causing obstructive hydrocephalus (Figure 1). No evidence of leptomeningeal spread was observed on initial imaging. The patient underwent near-total surgical resection of the tumor, achieving maximal safe excision without neurological compromise. Histopathological evaluation confirmed classic medulloblastoma [3-6].

Molecular analysis performed using a targeted next-generation sequencing panel revealed the SHH subgroup with a PTCH1 mutation. Immunohistochemical staining supported this classification, demonstrating elevated expression of GLI1, a downstream effector of SHH signaling. These findings suggested potential responsiveness to SHH pathway inhibition, informing subsequent adjuvant therapy decisions.

METHODS AND INTERVENTIONS

Following surgery, the patient received risk-adapted craniospinal irradiation, administered according to contemporary pediatric oncology protocols, with concurrent close monitoring for neurocognitive and endocrine effects. Post-radiotherapy, oral vismodegib, a selective SHH pathway inhibitor, was initiated at a dose of 150 mg daily for six months. Treatment was closely monitored with serial MRI imaging, routine laboratory assessments, and clinical follow-up to assess tolerability and therapeutic response [7].

Supportive care included neurocognitive assessments, endocrinologic evaluation for growth hormone deficiency or hypothyroidism, and management of common chemotherapy- and radiotherapy-associated symptoms, including nausea, fatigue, and alopecia. Emphasis was placed on multidisciplinary coordination among neurosurgery, pediatric oncology, neuro-oncology, and rehabilitation services to optimize patient outcomes.

RESULTS

Postoperative MRI demonstrated no residual enhancing tumor. The patient tolerated craniospinal irradiation and vismodegib therapy well [8]. Mild adverse effects were observed, including fatigue, alopecia, and transient mild nausea (Figure 2), which resolved without intervention. Serial MRI imaging at 3- and 6-month intervals showed stable disease with no evidence of recurrence. Neurocognitive assessments revealed age-appropriate development, and quality-of-life measures remained preserved throughout the follow-up period.

Molecular-targeted therapy resulted in suppression of SHH pathway signaling, as evidenced by reduced GLI1 expression on follow-up immunohistochemistry. No evidence of secondary malignancy or systemic toxicity was observed, supporting the safety and feasibility of incorporating SHH inhibitors into standard therapy regimens. Multidisciplinary follow-up emphasized ongoing surveillance for delayed toxicities, growth abnormalities, and long-term neurological sequelae [9].

Figure 2: Case Timeline with MRI Response to Vismodegib.

DISCUSSION

This case highlights the feasibility and clinical benefit of integrating molecularly guided targeted therapy into conventional treatment paradigms for SHH-subgroup medulloblastoma. SHH pathway inhibition complements surgical resection and radiotherapy by addressing tumor biology at a molecular level [10,11], potentially reducing recurrence risk and improving long-term disease control. The patient's favorable neurocognitive outcomes underscore the potential for targeted therapies to mitigate the long-term sequelae commonly associated with aggressive pediatric brain tumor treatment.

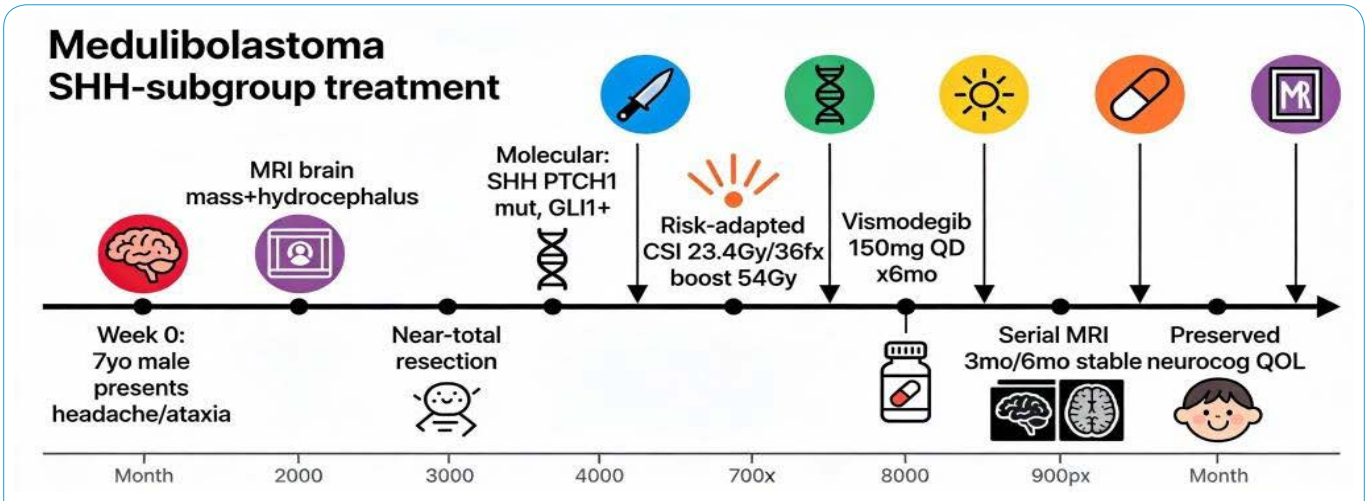

Figure 1: Medulloblastoma Molecular Subgroups Classification.

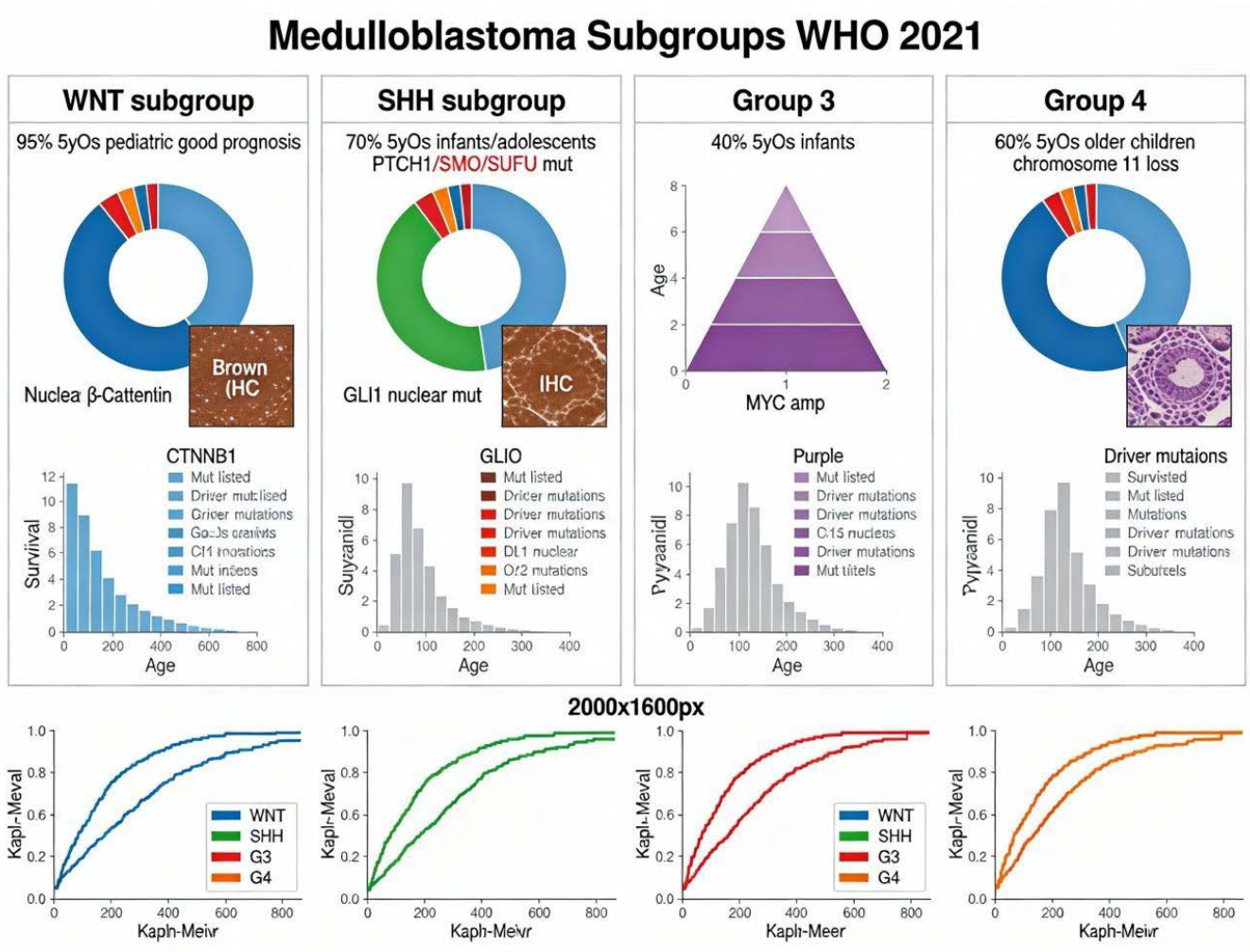

Figure 2: Case Timeline with MRI Response to Vismodegib.

Precision medicine in pediatric oncology enables risk-adapted therapy, minimizing unnecessary exposure to cytotoxic treatments while tailoring interventions to tumor-specific molecular vulnerabilities. Early molecular profiling is critical to identify candidates for pathway-specific therapy and to optimize treatment timing and sequencing. Although promising, the potential development of resistance to SHH inhibitors necessitates ongoing surveillance and consideration of combination therapies, including immunotherapy or epigenetic modulators.

Long-term studies are required to evaluate durability of response, late effects, and overall survival in larger cohorts. Nevertheless, this report provides evidence that precision-guided therapy can be safely implemented in a multidisciplinary care setting, offering a model for future case management and research initiatives [12].

This single-patient report cannot be generalized to all medulloblastoma subgroups. Short-term follow-up limits assessment of late toxicity, tumor recurrence, and long-term survival. Further studies involving larger [13], multicenter cohorts are needed to confirm safety, efficacy, and cost-effectiveness of targeted SHH therapy. Additionally, resistance mechanisms and optimal combination strategies remain under investigation.

CONCLUSION

Integration of molecularly guided targeted therapy into conventional treatment for SHH-subgroup medulloblastoma offers a promising approach to improving disease control while minimizing systemic and neurocognitive toxicity. Early genomic characterization is critical for tailoring therapy and guiding multidisciplinary care. Precision medicine strategies hold significant potential for optimizing outcomes in pediatric medulloblastoma and represent a paradigm shift in the management of complex neuro-oncologic diseases.

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