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CASO CLÍNICO

Infantile high-grade glioma with CLIP2-MET fusion mutation: a case report and therapeutic challenges

Glioma infantil de alto grado con mutación de fusión CLIP2-MET: informe de un caso y desafíos terapéuticos

»Jheremy Sebastian Reyes Barreto [1]
»Raul Fernando Vega Alvear [1]
»Juan Sebastian Aguirre Patiño [1 2]
»Sofia Catalina Velasco Sandoval [2]
»Oscar Eduardo González Figueredo [2]

[1] Cancer and Molecular Medicine Research Group (CAMMO), Bogotá, Colombia.
[2] Fundación Santa Fe de Bogotá, Bogotá, Colombia.

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Abstract

Introduction: Infantile high-grade gliomas are rare malignancies of the central nervous system (CNS) in children. Despite advancements, significant challenges remain in their treatment. A better understanding of their molecular biology may provide new therapeutic options. **Clinical case:** We report the case of a 30-month-old female diagnosed with an infantile high-grade glioma. Following urgent surgical resection, molecular analysis via a fusion panel identified a CLIP2-MET fusion mutation. This finding suggested potential treatment with crizotinib, a targeted therapy. However, several barriers delayed treatment initiation, including the lack of approval for crizotinib use in CNS tumors in Colombia and concerns about interactions with anticonvulsant therapy. Despite a brief period of clinical stability after initiating treatment, the patient unfortunately succumbed to the disease. **Conclusion:** Infantile high-grade gliomas pose significant therapeutic challenges, but identifying specific gene fusions, such as CLIP2-MET, may open new avenues for targeted therapy. This case underscores the need for regulatory adaptations to facilitate access to promising treatments when evidence supports their potential efficacy. To our knowledge, this is the first case in Colombia where an infantile glioma was treated with crizotinib, highlighting both the promise and the challenges of precision medicine in pediatric oncology.

*** Autor para correspondencia:** Jheremy Reyes. Cancer and Molecular Medicine Research Group (CAMMO).
Correo electrónico: js.reyesb@uniandes.edu.co
Doi: https//doi.org/10.51643/22562915.745

Keywords: glioma; gene fusion; molecular targeted therapy; receptor protein-tyrosine kinases.

Resumen

Introducción: Los gliomas infantiles de alto grado son malignidades poco frecuentes del sistema nervioso central (SNC) en niños. A pesar de los avances, el tratamiento de estos tumores aún enfrenta importantes desafíos. Una mejor comprensión de su biología molecular puede ofrecer nuevas opciones terapéuticas. **Caso clínico:** Presentamos el caso de una paciente de 30 meses diagnosticada con un glioma infantil de alto grado. Tras una resección quirúrgica urgente, un panel de fusión reveló una mutación de fusión CLIP2-MET, lo que sugirió un tratamiento con crizotinib. Sin embargo, surgieron varios obstáculos antes de iniciar la terapia dirigida, como la falta de aprobación de crizotinib para tumores del SNC en Colombia y el riesgo de interacción con la terapia anticonvulsiva. A pesar de lograr una breve estabilidad clínica tras el inicio del tratamiento, la paciente tuvo un desenlace fatal. **Conclusión:** Los gliomas infantiles de alto grado representan un desafío terapéutico significativo, pero la identificación de fusiones génicas específicas, como CLIP2-MET, puede abrir nuevas oportunidades para terapias dirigidas. Este caso destaca la necesidad de adaptar las regulaciones para facilitar el acceso a tratamientos prometedores cuando existe evidencia de su eficacia potencial. Hasta donde sabemos, este es el primer caso en Colombia en que un glioma infantil fue tratado con crizotinib, lo que resalta tanto el potencial como las dificultades de la medicina de precisión en oncología pediátrica.

Palabras clave: glioma; fusión génica; terapia molecular dirigida; proteínas tirosina quinasas receptoras.

Introduction

Infantile high-grade gliomas (iHGGs) are rare and aggressive central nervous system (CNS) tumors in children under three years of age, characterized by rapid progression and limited treatment options.[1-3] Despite significant strides in understanding their molecular biology, these tumors remain challenging due to their genetic heterogeneity. One emerging target in iHGGs is the CLIP2-MET fusion mutation, a genetic alteration that leads to constitutive activation of the MET pathway, promoting tumor growth and proliferation through aberrant signaling in the MAPK and PI3K/AKT pathways.[4, 5] This mutation results in continuous tyrosine kinase activity, driving oncogenesis and making MET a promising target for therapeutic intervention.

Current treatment strategies for iHGGs typically include a combination of surgical resection, radiation therapy, and chemotherapy.[1] However, these approaches often yield limited success due to the tumor's intrinsic resistance and the vulnerability of the pediatric brain. Targeted therapies, particularly tyrosine kinase inhibitors (TKIs), have shown potential in addressing specific genetic mutations such as CLIP2-MET fusions. Crizotinib, a dual ALK and MET inhibitor, works by selectively binding to the ATP-binding site of the MET receptor, inhibiting its phosphorylation and subsequent downstream signaling. This inhibition can reduce tumor cell proliferation and promote apoptosis in tumors with MET gene alterations.[6-8]

In this case report, we present a 30-month-old female patient with an iHGG harboring a

CLIP2-MET fusion mutation. The therapeutic approach included off-label use of crizotinib, highlighting the potential of precision medicine. However, challenges such as drug approval barriers and pharmacological interactions with anticonvulsants complicated the treatment process. This case underscores the importance of expanding access to targeted therapies and optimizing regulatory pathways to improve outcomes for patients with rare pediatric brain tumors.

Clinical case

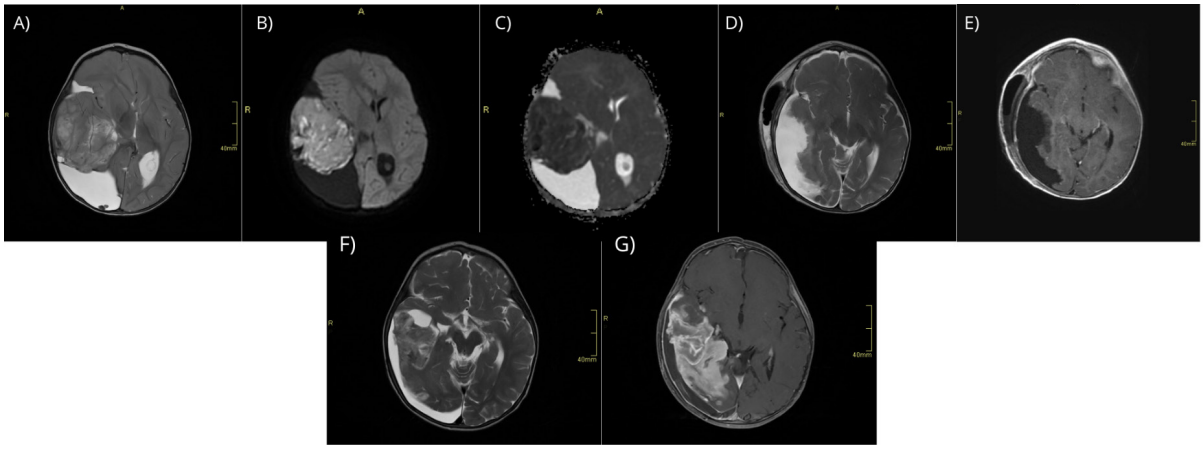
A 30-month-old female with a history of neonatal cerebral venous sinus thrombosis and right hemispheric chronic subdural hematoma—likely related to maternal SARS-CoV-2 infection—was previously treated with a nine-week course of enoxaparin, resulting in complete resolution of thrombosis.

At 14 months of age, she presented with focal seizures affecting the left side. Brain MRI revealed an extra-axial hemorrhagic collection in the right temporo-parietal region and stable septate arachnoid cysts, with persistent midline shift—sequelae of the prior hematoma. Seizures were controlled with levetiracetam and oxcarbazepine.

One month later, she returned with vomiting, irritability, fatigue, and diarrhea. A new MRI revealed a rapidly growing, infiltrative, heterogeneous mass with solid and cystic components in the right frontotemporal region, causing uncal and subfalcine herniation (Figure 1A-C). This prompted urgent surgical resection.

Figure 1.

Magnetic resonance imaging (MRI) of the brain in sequences with T2-weighted information (A, D, F), DWI (B), ADC (C), and T1 with contrast (E and G).



Note: The initial exophytic right frontotemporal lesion is observed, lacking a cleavage plane with the adjacent brain parenchyma (A), showing diffusion restriction (B and C). Contrast-enhanced images were not available in the initial study. In the post-surgical study, adequate resection of the lesion is demonstrated, with the surgical cavity showing no abnormal enhancement after contrast administration (E). During follow-up, disease progression is noted with the appearance of lesions in the right frontal, temporal, parietal, and occipital regions, showing heterogeneous high signal (F) and heterogeneous enhancement. Frontal involvement is not demonstrated in the image.

Intraoperatively, a large temporo-parieto-occipital mass with cystic changes, neovascularization, and necrosis was identified. Cryosection suggested glial origin. Resection was completed uneventfully. Postoperative imaging confirmed complete resection (Figure 1D-E), and CSF cytology and a CNS tumor fusion panel were obtained.

Histopathology confirmed a WHO grade 4 infantile high-grade glioma. The patient was started on the Baby POG (POG923) protocol while awaiting molecular results. A second pathological review was performed at Children's National Hospital, and methylation profiling was conducted at the NIH. Valproic acid was added to the chemotherapy regimen for its potential sensitizing effect.

Initial molecular results showed low microsatellite instability, a tumor mutational burden of 1.08 mutations/Mb, and no actionable mutations. Two months later, follow-up imaging revealed multifocal recurrence (Figure 1F-G). Due to tumor distribution, bleeding risk, and potential neurological injury, re-resection was not feasible, and palliative care was initiated.

Subsequent NIH profiling identified a CLIP2-MET gene fusion. Crizotinib—a dual ALK and MET inhibitor with activity in MET fusion tumors—was proposed. However, it is not approved for CNS tumors in Colombia. Off-label access was pursued, alongside lacosamide for refractory epilepsy, which also required special authorization due to age restrictions.

After adjusting anticonvulsant therapy, crizotinib was initiated at 30 mg/kg/day in two divided doses. Clinical improvement followed, with resolution of seizures and decreased irritability.

Unfortunately, six weeks later, the patient presented with signs of intracranial hypertension. Imaging showed extensive tumor progression, leading to rapid clinical decline and death.

Discussion

Infantile brain tumors represent less than 10% of all pediatric central nervous system tumors, with iHGGs being an exceptionally rare and aggressive subgroup.[4]. Despite global improvements in pediatric cancer outcomes, infants diagnosed with iHGGs continue to experience high early mortality, largely due to the tumor's rapid progression, limited therapeutic options, and the challenges posed by the immature central nervous system.[4, 5]

Unlike adult gliomas, iHGGs frequently harbor gene fusions as primary oncogenic drivers, with the mesenchymal-epithelial transition (MET) gene being recurrently involved.[5, 6] MET fusions activate downstream signaling pathways such as MAPK and PI3K/AKT, promoting proliferation, survival, and resistance to apoptosis.[3, 6] A large-scale analysis of over 75,000 cancer patients found MET fusions in 0.15% of gliomas.[7] while another study of 118 pediatric patients identified MET-related tyrosine kinase receptor anomalies as key alterations in a subset of iHGGs.[7]

The MET gene encodes c-Met, a receptor tyrosine kinase that plays a pivotal role in tumorigenesis. When fused with partners such as PTPRZ1, TFG, or CLIP2, the resulting chimeric proteins exhibit constitutive kinase activity.[3, 6] CLIP2, specifically, encodes a cytoplasmic linker protein involved in microtubule dynamics and vesicular trafficking [8]. In CLIP2-MET fusions, loss of the autoregulatory domain leads to persistent activation of the MET pathway. [2, 3, 9, 10] thereby establishing a rational target for TKIs.

While rare, CLIP2-MET fusions are clinically actionable. Preclinical studies and limited clinical data suggest sensitivity to TKIs such as crizotinib, ceritinib, capmatinib, tepotinib, and newer-generation inhibitors like lorlatinib and ensatinib, which exhibit better CNS penetration.[7, 11, 12]. Crizotinib, in particular, inhibits both ALK and MET by blocking their ATP-binding sites and has shown promise in pediatric patients with MET-driven tumors.[13]

To our knowledge, this is the first reported case in Colombia of a pediatric glioma harboring a CLIP2-MET fusion treated with crizotinib. Although the patient experienced brief seizure control and clinical stabilization, rapid tumor progression followed. This mirrors a similar case of an 8-year-old with a PTPRZ1-MET fusion-positive cerebellar glioblastoma who initially responded to crizotinib but later developed resistant disease, ultimately leading to death.[5,]

Such outcomes underscore the intratumor heterogeneity of iHGGs, a key factor contributing to resistance and therapeutic failure.[14] The evolving nature of fusion-positive gliomas demands combination approaches and real-time molecular monitoring to anticipate resistance mechanisms. Despite the availability of molecular diagnostics, treatment success also depends on timely access to therapy.

Our experience highlights important regulatory barriers. In Colombia, crizotinib is approved only for adult lung cancer, necessitating off-label authorization for pediatric CNS use. Similarly, lacosamide, required to manage the patient's refractory epilepsy, lacks approval for children under four years of age. These bureaucratic delays postponed treatment initiation and reflect systemic challenges in low- and middle-income countries. There is an urgent need to establish more agile regulatory frameworks that enable rapid, evidence-informed access to promising therapies for rare pediatric malignancies.

Conclusion

Infantile high-grade gliomas with CLIP2-MET fusion are extremely rare but potentially actionable tumors. This case highlights the value of early molecular profiling to identify candidates for targeted therapy, such as crizotinib. However, the rapid disease progression despite treatment reflects the intrinsic heterogeneity and resistance mechanisms of iHGGs. Additionally, the delays caused by regulatory barriers underscore the urgent need for more flexible approval pathways for off-label use in pediatric oncology. Enhancing timely access to personalized treatments is critical to improving outcomes in children with rare and aggressive CNS tumors.

Abbreviation list

CNS – Central Nervous System

ED – Emergency Department

EGFR – Epidermal Growth Factor Receptor

iHGG – Infantile High-Grade Glioma

INVIMA – Instituto Nacional de Vigilancia de Medicamentos y Alimentos (Colombia's National Institute for Food and Drug Surveillance)

MRI – Magnetic Resonance Imaging

MET – Mesenchymal-Epithelial Transition Factor

NIH – National Institutes of Health

POG923 – Pediatric Oncology Group Protocol 923 (Baby POG)

SARS-CoV-2 – Severe Acute Respiratory

Syndrome Coronavirus 2

TKI – Tyrosine Kinase Inhibitor

WHO – World Health Organization

Consent for publication

Obtained

Ethics Approval and Consent to participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and relevant national and international regulations for research involving human subjects. The Cancer and Molecular Medicine Research Group (CAMMO) Ethics Committee reviewed and approved this case report. Written informed consent was obtained from the patient's legal guardians for the collection and publication of medical data, including the use of anonymized clinical images. All efforts were made to ensure patient confidentiality, and no identifiable information is disclosed in the manuscript. This report was prepared with the highest ethical standards to contribute to the understanding and management of infantile high-grade gliomas.

Conflicts of interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Competing Interest

The authors declare that they have no competing interests.

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Author's Contributions

Contributors played a substantial role in conception, design, acquisition, analysis, interpretation, writing, and critical review of the manuscript. All authors approved the final content and accepted responsibility for its accuracy and integrity.

Author's Bio

Jheremy Reyes Barreto. Medicina, Universidad de Los Andes, Colombia

Raúl Fernando Vega. Medicina, Universidad del Norte.

Juan Sebastián Aguirre. Médico general, maestrante en teología de la Biblia.

Sofía Catalina Velasco. Médica Radióloga.

Oscar Eduardo González. Hematólogo y Oncólogo Pediatra

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