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Pediatric Neurosurgery

Pediatr Neurosurg , DOI: 10.1159/000535842

Received: June 21, 2023

Accepted: December 7, 2023

Published online: December 18, 2023

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ISSN: 1016-2291 (Print), eISSN: 1423-0305 (Online)

https://www.karger.com/PNE

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A Case Report of Infant-type Hemispheric Glioma with a Novel GAB1-ABL2 Kinase Fusion Treated with Dasatinib

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Short Title: INFANT-TYPE HEMISPHERIC GLIOMA WITH NOVEL GAB1-ABL2 FUSION

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Number of Tables: 0

Number of Figures: 11

Word count: 2,444

Keywords: Infant-type hemispheric glioma, high-grade, gene fusion, targeted therapy

Established Facts and Novel Insights

Established Facts

· Infant-type Hemispheric Glioma is a rare form of cancer that affects the cerebral hemispheres of newborns and infants.

· Currently, there is no standardized treatment protocol for Infant-type Hemispheric Glioma.

· In the absence of a targetable gene fusion, surgery is the main therapeutic strategy, which contributes to patient morbidity and poses a challenge for tumor control near eloquent brain areas.

Novel Insights

· The GAB1-ABL2 kinase fusion is a novel genetic alteration that has not been previously reported in the literature.

· Dasatinib is an effective targeted therapy for Infant-type Hemispheric Glioma harboring a GAB1-ABL2 fusion.

· This finding expands the genotypic spectrum and treatment options of Infant-type Hemispheric Glioma.

Abstract

Introduction: Infant-type hemispheric glioma (IHG) is a rare form of cancer that affects newborns and infants. It is classified as a pediatric-type high-grade glioma and typically harbors receptor tyrosine kinase (RTK) gene fusions. Here, we present the finding of a novel gene fusion IHG treated with a targeted therapy that has yet to be implemented for any other IHG case to date.

Case Presentation: We report the case of a 12-month-old boy with IHG who presented with obstructive hydrocephalus due to a large mass in the right frontal lobe. The patient initially underwent mass resection, but subsequent imaging showed rapid interval progression of the residual tumor. Comprehensive molecular analysis of the tumor tissue revealed a novel GAB1-ABL2 gene fusion, and the patient was started on dasatinib, an ABL kinase inhibitor. Shortly after initiation of dasatinib treatment, there was a significant reduction in tumor size and enhancement, followed by stabilization of disease.

Discussion: The patient's robust response to treatment suggests that dasatinib is an effective targeted therapy for IHG harboring a GAB1-ABL2 gene fusion. This finding may inform future investigations into the disease processes of IHG and help guide the diagnosis and treatment of IHG in the absence of previously identified gene fusions, improving clinical management of this vulnerable patient population.

Introduction

Central Nervous System (CNS) tumors are the second most common cancers affecting pediatric patients [1]. Infant-type Hemispheric Glioma (IHG) is a novel and rare CNS tumor. In the 2021 WHO classification of tumors of the central nervous system, IHG is categorized as a pediatric-type diffuse high-grade glioma [2]. It occurs in the cerebral hemispheres of newborns and infants and typically harbors a distinct molecular profile with receptor tyrosine kinase (RTK) fusion genes involving the neurotrophic receptor tyrosine kinase (NTRK) family, ROS1, ALK, or MET [3, 4].

Treatment of IHG presents a challenge to clinicians due to the vulnerable patient population, limited knowledge of the disease, and ambiguous treatment options. Currently, surgery is the main therapeutic strategy, aiming for gross total resection of the tumor. Chemotherapy and radiation have historically limited efficacy in IHG [5]. However, target-driven therapies have been shown to be effective in promoting long-term survival in IHG patients with targetable genetic alterations. For instance, the tyrosine kinase inhibitor lorlatinib has been reported to successfully treat tumor tissue harboring ALK gene fusions [6]. Due to the high response rate of kinase fusion positive tumors to targeted agents, these cases usually have better outcomes than fusion negative cases [3].

Here, we describe the case of a patient found to have a novel GAB1-ABL2 fusion IHG that was treated effectively with the targeted therapy dasatinib. To our knowledge, this fusion has yet to be documented in the literature. This report may help identify and treat future IHG cases with similar gene fusions.

Case Presentation

The patient is a 12-month-old male with a history of intraventricular hemorrhage (IVH), retinopathy of prematurity, and anemia of prematurity, who presented to the ED with obstructive hydrocephalus at 3 months old. He was delivered at 25 weeks gestational age via an emergent C-section, which was followed by a 2.5 month stay in the NICU due to respiratory failure requiring intubation and subsequent CPAP. Prior to admission, a head ultrasound showed a new midline shift, prompting his PCP to send him to the ED for further evaluation. In the ED, the patient's physical exam was notable for bulging anterior and posterior fontanelles and sunsetting eyes. MRI brain (shown in Fig. 1, 2) revealed a lobulated heterogenous mass in the right frontal lobe with local mass effect, midline shift, subfalcine herniation, and effacement of frontal horns and lateral ventricles. On further analysis, the lesion was found to be necrotic and cystic with enhancing nodularity. Findings were compatible with neoplasm.

In order to diagnose and manage the lesion, surgery was pursued. One week after initial presentation, the patient underwent a right pterional craniotomy for mass resection. The tumor was successfully resected in piecemeal, and the patient tolerated the procedure well. Figure 3 depicts postoperative imaging of the residual tumor left after resection.

One day after the procedure, the patient began displaying intermittent extensor posturing. CTH showed blood in the ventricles with increased ventricular size, and MRI revealed postoperative bleeding, increase in hydrocephalus, and right middle cerebral artery infarct. These findings were inconsistent with the findings postoperatively and hemostasis was achieved after quite some time.

The patient subsequently underwent evacuation of the hematoma, and right frontal external ventricular drain (EVD) placement. He was maintained on seizure precautions with levetiracetam during this time and serial CT images were stable without additional hemorrhage. Two weeks later, the EVD was removed and replaced with a ventriculoperitoneal shunt (VPS) during an uncomplicated procedure. Subsequent imaging is shown in Figure 4.

Histopathological evaluation of the resection specimen showed a morphologically heterogenous glial neoplasm. Areas with high grade features (Fig. 5 a, b, f) were evident and included increased cellularity, pleomorphic tumor cells, frequent mitotic figures, markedly elevated proliferation index (approximately 40-50% in regions), microvascular proliferation with hyperplasia, and foci of tumor necrosis. Additionally, there were areas of lower cellularity characterized by the presence of spindle-shaped tumor cells arranged in whorling, storiform patterns with desmoplasia (Fig. 5 c and d), features reminiscent of that seen in desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma. Immunohistochemical staining showed variable positive staining of the tumor cells for glial fibrillary acidic protein (GFAP), confirming the glial nature of the neoplasm. The neoplastic cells were immunohistochemically negative for synaptophysin, chromogranin, epithelial membrane antigen (EMA), neuronal nuclear antigen (NeuN), desmin, smooth muscle actin (SMA), myogenin, IDH1-R132H, BRAF-V600E, D5F3-ALK, and ALK1.

DNA methylation array analysis showed the tumor to match the infant-type hemispheric glioma methylation class (calibrated score 0.99). Evaluation for gene fusions performed by an outside institution using Archer analysis came back negative. This testing consisted of a panel of 123 cancer related genes previously reported to be involved in chromosomal rearrangements.

Unfortunately, rapid interval progression of the residual tumor was found postoperatively (shown in Fig. 6, 7). A repeat CTH two weeks after VPS placement revealed an enlarged nodule along the inferior margin of the resection cavity, measuring 3 cm in greatest dimension. This was a significant increase from two weeks prior, when it had measured only 1.7 cm. MRI brain confirmed the enlarged residual multifocal tumor in the right frontal lobe. These findings were concerning for recurrence of disease and were highly unexpected given their rapid nature.

In the absence of a targetable fusion, the only option for adjuvant therapy was high dose chemotherapy, which was considered too risky given the patient's history of prematurity and IVH. Instead, the team decided to move forward with close clinical observation and consistent MRI surveillance imaging.

At this time, comprehensive RNA sequencing analysis of the tumor tissue performed by CARIS Life Sciences detected a novel GAB1-ABL2 fusion. The report found that exon 6 of GAB1 was joined with exon 2 of ABL2. Thus, ABL kinase inhibitors were considered for treatment. Since dasatinib has greater CNS penetration compared to the other agents that are safe for infants, this therapy was chosen to treat the patient's residual disease, with a curative goal. He was immediately started on oral dasatinib with body surface area based dosing at 15.6mg (4.7ml) or 60mg/m^2/day compounded into a 3.3mg/ml solution delivered via nasogastric tube.

Shortly after initiation of dasatinib, an MRI brain showed reduction in size of the mass as well as cystic components. After this initial improvement, repeat imaging every two weeks showed stabilization of the disease, and the patient was ultimately discharged two months after admission. The tumor size remained stable after discharge.

On subsequent surveillance imaging, expansion of the nodule was observed. It increased in size from 1.4 x 1.9 cm to 2.2 x 2.6 cm. Although concerning, the slow expansion of the lesion was occurring in conjunction with decompression of the ventricular system due to the VPS, so it was unclear if the apparent expansion was true growth or apparent growth secondary to reduction of the ventricles. The MRI also showed interval resolution of abnormal enhancement within the mass. Two months later, repeat imaging (shown in Fig. 8, 9) revealed marked interval decrease in the size of the soft tissue mass in the right frontal lobe. Even further reductions in the lesion size and nodular enhancement were observed in the most recent imaging study (Fig. 10, 11), which showed the mass measuring up to 5 mm.

Going forward, the patient will be maintained on targeted dasatinib therapy with monthly follow-up for weight-based dose adjustments and surveillance imaging will be performed every three months.

Discussion

Here, we report a case of Infant-type Hemispheric Glioma with a novel GAB1-ABL2 gene fusion treated with a targeted therapeutic that has yet to be implemented for any other IHG case to date. IHG is a newly defined entity of the 2021 WHO classification of tumors of the central nervous system. Due to its novelty and rarity, our current knowledge of the disease is limited. It is classified as a pediatric-type diffuse high-grade glioma and often harbors RTK gene fusions [2-4]. IHG presents a clinical challenge due to the vulnerable patient population, diagnostic uncertainty, and ambiguous treatment options.

Infants have the highest incidence rates of CNS tumors, and gliomas are the most commonly occurring tumor type in this demographic [7]. Yet very little is known about infant gliomas. Furthermore, outcomes for these tumors are difficult to predict because they show paradoxical clinical behavior compared to gliomas in older children and adults. In infants, low-grade gliomas (LGG) have higher mortality rates, while high-grade gliomas (HGG) usually have better outcomes [4]. In fact, long-term overall survival in patients with HGG is more favorable in infants compared with older children [4, 8, 9]. This leads to uncertainty when it comes to treatment because it is unclear whether clinicians should pursue aggressive measures.

Currently, there is no standardized treatment protocol for IHG. Surgery aiming for gross total resection (GTR) is the main therapeutic strategy since chemotherapy and radiation have historically limited efficacy in IHG and are associated with long-term complications [5]. Surgery provides samples for histological evaluation and molecular profiling of the tumor, which is necessary for an accurate diagnosis of IHG. Extent of resection is closely correlated with prognosis, with gross total resection associated with prolonged survival [10]. However, depending on the size and location of the tumor, gross total resection is not always achievable. The infant skull is highly plastic, so IHG tumors typically grow quite large before patients become symptomatic due to increased intracranial pressure. Large

tumors lead to distortion of brain vasculature, which can increase the risk of hemorrhage during and after surgery. Additionally, infants are more vulnerable to hypovolemic shock and cardiac arrest from blood loss during surgery due to their low circulating volume. Anesthesiologic risks must also be taken into consideration for this patient demographic. However, alternative treatments like radiation therapy carry even greater risk. Radiation is usually avoided in IHG because children under three years of age are more vulnerable to serious sequelae such as developmental delay, endocrine dysfunction, and secondary neoplasms in the CNS [1].

Considering the morbidity and mortality of treatments discussed thus far, the search for novel genetic alterations and target-driven therapies is critical to promote survival in IHG patients. Historically, mutations involving ALK, ROS1, NTRK1/2/3, and MET have been reported in IHG [1, 3-6, 8, 11-14]. This group of RTK gene fusions is present in 61-83% of IHG cases [3, 4]. Shahab et al. reported the case of a patient with IHG harboring an ATIC-ALK gene fusion, which responded well to the ALK inhibitor lorlatinib [6]. Other reports have found that larotrectinib, a selective pan-TRK inhibitor, is an effective treatment for IHG harboring TPR-NTRK1 and ETV6–NTRK3 fusions [13, 14]. Overall, gene fusion-positive cases typically have better outcomes compared to their fusion negative counterparts [3]. Other gene fusions that have been identified are PPP1CB-ALK, TPM3-NTRK1, ZCCH8-ROS1, and CLIP2-MET [4, 7, 11].

The GAB1-ABL2 fusion found in our patient has never been reported in any other IHG case to date. It has also never been found in other types of cancer. There have been reports of a GAB1-ABL1 gene fusion in pediatric soft tissue perineuroma [15], but the GAB1-ABL2 fusion is unique. Fusions involving ABL1 are common in leukemias like CML, whereas ABL2 alterations are most commonly found in breast carcinoma, colon adenocarcinoma, lung adenocarcinoma, and cutaneous melanoma [16]. ABL2 plays an important role in neurulation, and it is required for adhesion-dependent neurite branching, synapse and dendrite stability, as well as fibroblastic and epithelial cell adhesion and migration [16]. GAB1 is involved with propagating signals that are essential for cell proliferation, motility, and erythroblast development [17]. The role of GAB1 in cancer is less clear than GAB2. The GAB1-ABL2 gene translocation codes for a constitutively active tyrosine kinase, which disrupts cell cycle regulation. Further investigation into this novel gene fusion is necessary to understand how it contributes to the disease process of IHG. It is possible that the unusual rapid recurrence of disease experienced by our patient could be a characteristic of this unique molecular profile.

The present case also demonstrated a novel application of the targeted agent dasatinib to treat IHG. Dasatinib is an inhibitor of ABL and SRC family tyrosine kinases and is typically used to treat patients with Philadelphia chromosome-positive (BCR-ABL) CML. However, its superior blood brain penetration and safety profile in infants made it the optimal choice for treatment of our patient's GAB1-ABL2 tumor. The rapid shrinkage of the tumor after initiation of dasatinib as well as the reduction in abnormal enhancement within the mass shows that dasatinib is an effective treatment for IHG harboring a GAB1-ABL2 fusion. This finding suggests that clinicians should look for this novel fusion in other IHG cases since it responds well to target-driven therapy.

CONCLUSION

This case report serves to advance our understanding of this rare disease, expanding the genotypic spectrum and treatment possibilities of IHG to enhance patient care. Multidisciplinary healthcare teams involving pediatric oncologists, neurosurgeons, and pathologists, among other specialists are essential to achieve the best outcomes for these patients with treatment plans that combine surgical

interventions, genetic and molecular analysis, and medical therapy. If surgical intervention is feasible, mass resection is often an important first step in treatment of IHG because it reduces tumor size and provides a tissue sample for comprehensive molecular profiling. This allows for greater diagnostic certainty and presents the possibility of treatment with targeted therapeutics such as dasatinib. Moving forward, more collaborative efforts are needed to investigate and decipher the biological basis of these rare tumors, identify new potential therapeutic targets, and further improve the clinical management of this vulnerable patient population.

Statements

Acknowledgement

None.

Statement of Ethics

Study approval statement: This study was reviewed and approved by the Albert Einstein College of Medicine and Montefiore Medical Center IRB, approval number 101407.

Consent to publish statement: Since the patient is a minor, written informed consent was obtained from the patient's mother, who was permitted to provide consent on behalf of the patient, for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received in the preparation of data for this manuscript.

Author Contributions

EBW, SC, and AK contributed to the composition of the manuscript. GJ, TK, RF, GL, SC, and AK contributed to the review of this manuscript. ND, MB, SC, AM, and AK were involved in the clinical care of the patient. EBW, AM, and AK were responsible for developing the concept for this manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. Preoperative MRI sagittal showing the initial tumor found at presentation.

Fig. 2. Preoperative MRI axial with heterogenous right frontal lobe mass.

Fig. 3. Postoperative MRI following mass resection.

Fig. 4. Postoperative MRI after shunt placement.

Fig. 5. (a) Low magnification view of an area exhibiting high grade glioma features including microvascular proliferation with hyperplasia (arrowheads). * (b) High magnification view showing pleomorphic high grade glioma cells and frequent mitotic figures (arrowheads). ** (c) Low magnification view from an area of the tumor with lower cellularity and spindle-shaped tumor cells arranged in whorled patterns. (d) A silver stain demonstrates the reticulin-rich, desmoplastic nature of the low cellularity regions. (e) In contrast, the high-grade cellular regions only show reticulin associated with the proliferated microvasculature. (f) Immunohistochemical staining for proliferation marker Ki67 shows a high proliferation index with numerous positively stained (brown) tumor cell nuclei.

*Stains: panels a, b, c = hematoxylin-eosin; panels d, e = silver stain for reticulin fibers; and panel f = immunoperoxidase stain for proliferation marker Ki67.

**The scale bar in panels a, c, d, e, and f represents 100 microns and in panel b 50 microns.

Fig. 6. Postoperative T2 weighted MRI showing tumor regrowth.

Fig. 7. Postoperative T1 weighted MRI showing tumor regrowth.

Fig. 8. Postoperative T2 weighted MRI after dasatinib initiation showing tumor shrinkage.

Fig. 9. Postoperative T1 weighted MRI after dasatinib initiation showing tumor shrinkage.

Fig. 10. Postoperative MRI axial after 6 months of dasatinib treatment.

Fig. 11. Postoperative MRI sagittal after 6 months of dasatinib treatment.