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Case Report

Pediatric central nervous system (CNS) neuroblastoma: A case report

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ABSTRACT

Background: Neuroblastomas are rare tumors activated by the *FoxR2* gene commonly found in pediatric patients. Due to the novelty of these tumors, there is no standard diagnostic profile. However, they have been found to express *Olig2*, *MAP2*, *SOX10*, *ANKRD55*, and synaptophysin, and they can be identified with magnetic resonance imaging (MRI). Treatment with chemotherapy combined with stem cell rescue and craniospinal irradiation can improve non-infant patient outcomes.

Case Description: We report a case of a 2-year-old patient who was diagnosed with a neuroblastoma through MRI imaging and pathology that confirmed *FoxR2* gene activation. The tumor was successfully removed. However, the tumor was not high-grade like most *FoxR2* neuroblastomas.

Conclusion: The unusual presentation of a low-grade *FoxR2* neuroblastoma demonstrates the necessity to conduct further research into the characteristics of these tumors.

Keywords: Central nervous system (CNS) neuroblastoma, FoxR2, Neuroblastoma, Pediatric neuroblastoma

INTRODUCTION

The class of tumors known as central nervous system primitive neuroectodermal tumors (CNS-PNET) has been changed due to heterogeneity of the genetic structure of tumors. Now, the tumor class has been divided into CIC rearranged sarcoma (CNS-SARC-CIC), CNS tumor with BCOR internal tandem duplication (CNS-BCOR-ITD), embryonal tumor with multilayered rosettes, *FoxR2* activated CNS neuroblastomas (CNS-NB-FOXR2), and CNS embryonal tumor not elsewhere classified or otherwise specified (CNS-ET-NOS/NES).[9] CNS-NB-FOXR2 are rare tumors to the point that epidemiological data are not complete, but it is known to primarily affect children with a peak incidence at 5 years of age.[4] Little is definitively known about CNS-NB-FOXR2, though they are believed to arise from neuroectodermal cells, which have a dual growth pattern in clusters of poorly differentiated embryonal cells alternating with cells of clear cytoplasm that show neurocytic differentiation in a fibrillary matrix, and they are rare cortical medulloblastomas.[1,4]

Diagnosis of CNS-NB-FOXR2 based on the DNA methylation profile is the most feasible option.[8,11] There was extensive *Olig2*, *MAP2*, and synaptophysin expression with the exclusion of high-grade gliomas found in these tumors.[3,4,8,11] Expression of *SOX10* and *ANKRD55* discriminates CNS-NB-FOXR2 from other CNS-PNET tumors, which can be detected with immunohistochemistry.[3,6] Next-generation sequencing shows structural rearrangement and fusion of the *FoxR2* transcription factor, leading to an overexpression of *FoxR2*.[1,3] Almost all tumors have a 1q chromosomal gain.[3] With the recency of the World Health Organization (WHO) classification, there has yet to be a standard imaging profile for CNS-NB-FOXR2. Magnetic resonance imaging (MRI) has found that these tumors almost always contain a mix of solid and cystic or necrotic components, the white matter was always involved, and the tumors are exclusively located in the supratentorial region.[4,11] Previous cases in the literature have been listed [Table 1].

The core therapy for neuroblastoma is "five or six cycles of effective multi-agent induction chemotherapy, surgery, radiotherapy at least to the primary tumor bed, and SCT followed by oral isotretinoin."[2] The main treatment modalities for neuroectodermal tumors (CNS-PNET) are similar to the treatment for medulloblastomas, which is craniospinal irradiation (CSI) with a focal boost, along with high-dose chemotherapy. The chemotherapy includes drugs such as methotrexate, cisplatin, etoposide, topotecan, cyclophosphamide, vincristine, and vinblastine if needed. These drugs can also be given continuously over low doses with a metronomic therapy. Although CSI is the current standard of treatment for CNS-PNET tumors for non-infant patients, it has shown no survival benefit for neuroblastoma tumors in infants. According to this study, older children should have treatment, including CSI, and younger patients who are less than three should be treated with a CSI-sparing protocol along with radiation therapy focal consolidation. In this paper, for patients with a FOXR2-activated CNS neuroblastoma, four out of six patients had 5 years of survival with no eventful circumstances, and five out of six patients had survived overall. The patient who died had only received chemotherapy and no CSI. The other patient who relapsed out of the six patients was saved through CSI therapy. Out of the five patients who overall survived, three of the five patients received focal radiation therapy along with chemotherapy, while two of them only received CSI (one as primary, the other as a salvage therapy).[9] In another study, one patient who was 2½ years old received the typical medulloblastoma treatment of CSI despite being so young, yet this patient survived for 5 years without relapse.[8] Another young patient in the same study did not receive any radiotherapy treatment and relapsed within 1 year and died afterwards. Local resection is also possible for smaller localized tumors.[3]

To increase the doses of chemotherapy for neuroblastoma, stem cell therapies are used to keep the bone marrow able to tolerate the additional therapy. The patient's cells are harvested before chemotherapy and given afterwards, also known as stem cell rescue.[2] Overall, this points to the importance of CSI and radiation in treating neuroblastoma

Table 1: Summary of previously reported cases of neuroblastoma.

Title	Author	Case Summary
Pediatric ependymoma	Pollock *et al*.[10]	A 2-year-old boy presented with worsening unsteady gait, expansive WHO Grade 3 ependymoma found filling the fourth ventricle, tumor found loss of H3K27me3 expression, treated with adjuvant radiotherapy.
Molecular classification and outcome of children with rare CNS embryonal tumors: Results from St. Jude Children's Research Hospital including the multi-center SJYC07 and SJMB03 clinical trials.	Liu, *et al*.[9]	Seventy children with histologically confirmed CNS-PNETs were separated based on different clinical characteristics (Ex, DNA Methylation) and split into craniospinal irradiation therapy or without irradiation. The 5-year and overall survival varied: CNS-NB-FOXR2: 66.7%/83.3%, CNS-SARC-CIC: 57.1%, HGNET-BCOR had low response to only chemotherapy but improved on radiation: 53.6%, ETMR/HGG/GBM did not respond well to either.
Molecular identification of CNS NB-FOXR2, CNS EFT-CIC, CNS HGNET-MN1, and CNS HGNET-BCOR pediatric brain tumors using tumor-specific signature genes.	Lastowska, *et al*.[8]	New genetic profiles of CNS tumors were identified being CNS NB-FOXR2, CNS EFT-CIC, CNS HGNET-MN1, and CNS HGNET-BCOR. Fourteen of these tumors were found in a pool of 187 using a new NanoString diagnostic method. These tumors are similar to other tumors of this category, which makes diagnosing using histology and immune markers more useful. CNS HGNET-MN1 and CNS NB-FOXR2 showed higher survival rates, and CNS HGNET-BCOR showed variability in survival.

WHO: World Health Organization, CNS: Central nervous system, CNS-PNETs: central nervous system primitive neuroectodermal tumors, DNA: Deoxyribonucleic acid, ETMR: Embryonal tumor with multilayered rosettes, ETMR: Embryonal tumor with multilayered rosettes, HGG: High grade glioma, GBM: Glioblastoma multiforme, HGNET: High-grade neuroepithelial tumor

of the CNS, especially for ones that are FOXR2 activated.[8,9] The postoperative status of patients with neuroblastoma is lacking in terms of information. One article showed that the patients with good survival rates received CSI along with maintenance dosing of chemotherapy but that future relapses would be more common in patients who received only focal irradiation. Therefore, local irradiation cannot be given to patients as a viable treatment option.[3]

HISTORY AND CASE PRESENTATION

JC is a 2-year-old African American male born full term at 38 weeks through C-section with a medical history of bronchiolitis who presented to the Emergency Department unresponsive and seizing. The patient's mother explained earlier that day that he could not ambulate and was in a trance, looking off in the distance at what she assumed was the television. He did not respond to verbal commands. The patient's father also noticed him shaking in his sleep the previous evening and attributed it to being cold from the A/C. On entering the room, the patient was unresponsive and actively seizing with eyes deviated to the right and focal seizure activity in both the right arm and leg and his mouth clamped down. He was found to be hypoxic, with an oxygen saturation of 85% and a rectal temperature of 100.2° F. He was given midazolam and levetiracetam on admission and started on lorazepam as needed for ongoing seizure activity. Initial computed tomographic (CT) imaging revealed a left inferior frontal mass concerning primary CNS neoplasm [Figure 1]. The following day, MRI confirmed the above findings as a cystic and solid mass lesion in the left inferior frontal gyrus associated with a cluster of enhancing microcystic lesions as well as a thick rim of restricted diffusion most conspicuous along the inferior medial aspect [Figure 2]. Based on the imaging findings, there was concern for a high-grade neoplasm such as anaplastic ependymoma or pilocytic astrocytoma (PCA). The MRI of the spine was unremarkable, with no evidence of abnormal enhancement.

Five days after presenting to the hospital, the patient was taken to the operating theater for a left frontal craniotomy and tumor resection. The tumor was encountered 0.5 cm deep to the insular cortex and was dusky and gray with a rich blood supply. It was easily removed with gentle suction. Specimens were sent to pathology with preliminary results indicating a high-grade neoplasm. He remained hemodynamically stable during the operation with no immediate complications and was extubated and admitted to the pediatric intensive care unit for postsurgical monitoring. Postoperative imaging the following day demonstrated expected interval changes related to the tumor resection and apparent residual enhancing tumor at the deep posterior margin in close proximation to the hypothalamus, anterior commissure, and anterior left optic tract [Figure 3]. The patient was discharged home on levetiracetam 3 days following his surgery with plans to follow up with neurosurgery, neurology, and oncology.

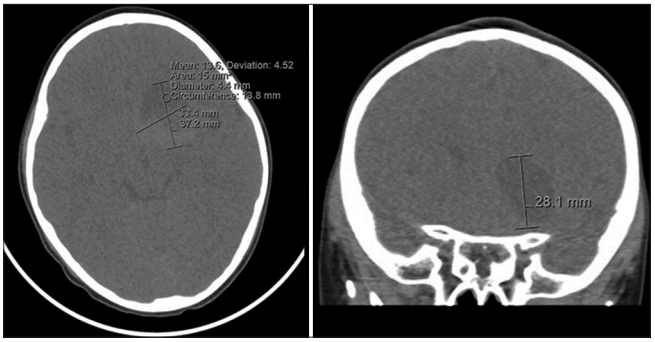

Figure 1: Initial computed tomographic reveals left inferior frontal mass measuring 3.7 × 3.3 × 2.8 cm.

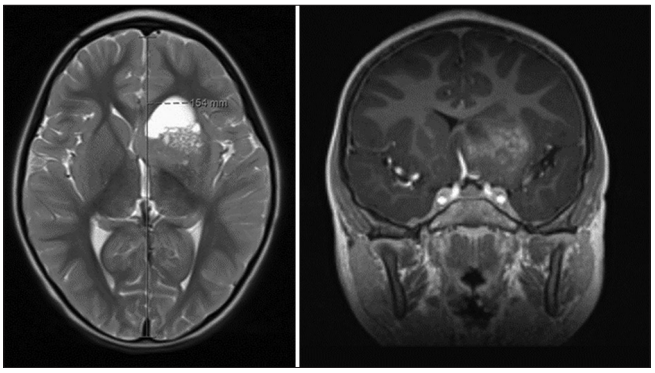

Figure 2: Follow-up magnetic resonance imaging demonstrating a cystic and solid mass lesion in the left inferior frontal gyrus associated with a cluster of enhancing microcystic lesions as well as a thick rim of restricted diffusion most conspicuous along the inferior medial aspect.

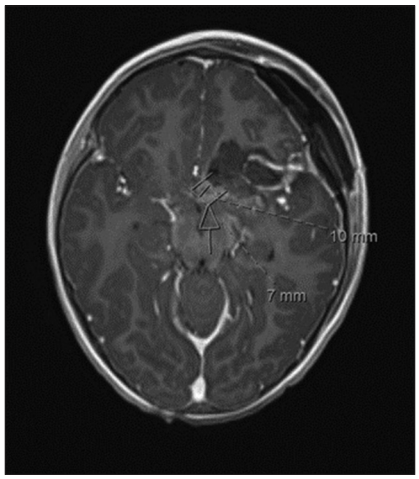

Figure 3: Postoperative magnetic resonance imaging the day following surgery demonstrating expective interval operative changes.

Preliminary pathology results from an outside institution (Mayo) demonstrated oligodendroglial-like neoplasm with scant mitoses, with loss of H3K27me3 expression. At this point, the Next generation sequencing (NGS) panel and microarray were still pending, and a referral was placed to an outside institution Mayo Clinic (UM) for neuro-oncology and neurosurgery second opinions. Final pathology results were available 2 weeks later that demonstrated a low-grade tumor but with inconclusive molecular results. A 6-week postoperative MRI demonstrated postsurgical changes related to the left frontal mass resection and ill-defined enhancement in the left subcallosal region at the deep posterior margin of the resection cavity consistent with residual tumor [Figure 4]. Complete pathology results confirmed a final diagnosis of CNS neuroblastoma, FOXR2 activated, and CNS WHO grade 4 [Figure 5]. Unusual in this case is the fact that the tissue does not show all the "high-grade features" one typically sees in CNS neuroblastoma with FOXR2 activated. The patient has since followed up with pediatric hematology oncology for intensive chemotherapy and radiation therapy with a potential of autologous stem cell transplant.

DISCUSSION

PCA and anaplastic ependymoma were initially of concern for this patient due to MRI and presentation pointing to a high-grade neoplasm. PCA and anaplastic ependymoma are the first and third most common central nervous system neoplasms in children, respectively.

Radiologically, PCAs are midline, well-circumscribed, and often infiltrate. While PCA is most commonly found in the cerebellum, these tumors can also occur in the optic tracts, brainstem, and cerebral hemispheres. However, when these tumors present in the cerebral hemispheres, the patient is typically a young adult.[7] This patient's MRI demonstrated a solid lesion with a rim of diffusion in the inferior medial aspect of the frontal gyrus, making PCA a likely diagnosis for this particular case. Presentation of a PCA can include symptoms related to mass effects, such as vomiting, which was not seen in this case. Lesions in the posterior fossa, vermis, and cerebellum can result in ataxia (peripheral and truncal) as well as gait changes.[7] This patient did not have worsening gait changes or ataxia rather difficulty ambulating for 1 day. Further, this patient presented due to seizure, which is uncommon in PCA presentation.

Anaplastic ependymomas can occur in all CNS locations and present nearly identically to this case. They are well-circumscribed tumors that present in young children as large supratentorial masses. Intracranial ependymomas often have areas of cysts, calcifications, and necrosis similar to the cystic and solid mass lesion noted on this patient's MRI.[5] In a Case Presentation from Memorial Sloan Kettering Cancer Center, a 2-year-old male was diagnosed with a grade III anaplastic ependymoma that filled the fourth ventricle. He presented due to concerns for worsening gait and ataxia over 2 months

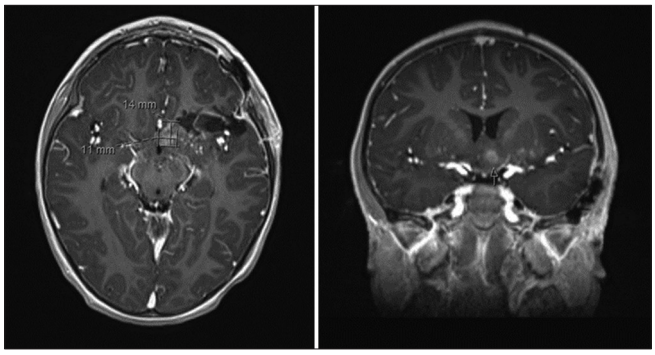

Figure 4: 6-week postoperative magnetic resonance imaging demonstrating an ill-defined enhancement in the left subcallosal region at the deep posterior margin of the resection cavity consistent with a residual tumor.

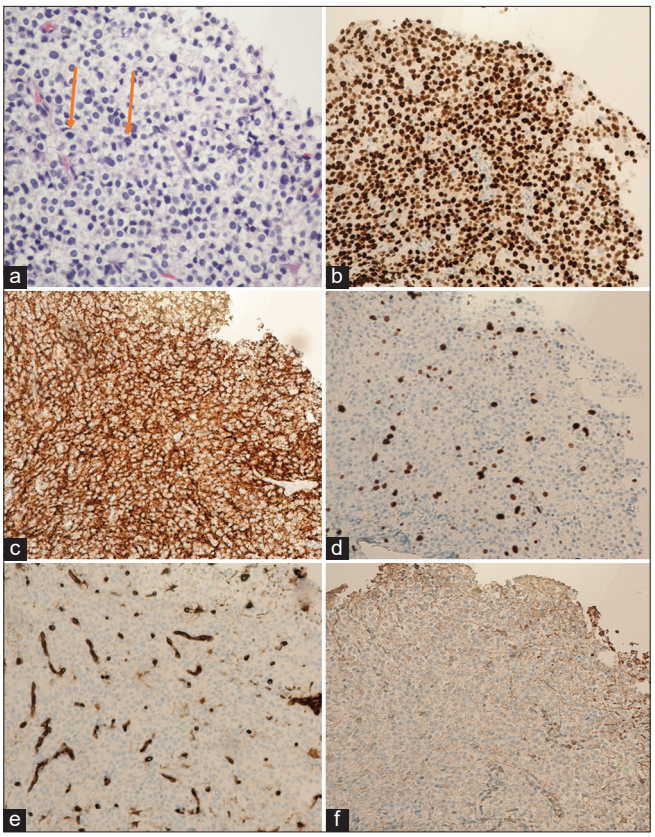

Figure 5: (a) Section shows the proliferation of small oval to round primitive neuronal cells with hyperchromatic, polygonal nuclei. The tumor shows scant mitotic activity (arrows highlight mitotic figures). (b and c) Tumor cells exhibit diffuse, strong immunoreactivity to OLIG2 and synaptophysin. (d) Tumor cells show moderate Ki-67 proliferation (8–10%). (e and f) Tumor cells exhibit negative immunoreactivity to Vimentin and glial fibrillary acidic protein (GFAP).

but was found to have a benign physical examination aside from minimal ataxia. He had normal strength, muscle tone, and neurologic examination.[10] This case involves a child of the same age, with no prior medical history, and who also had difficulty ambulating earlier in the day before he presented for seizure activity.

As this patient presented similarly to cases with PCA and anaplastic ependymoma, there was a significant concern for high-grade neoplasm, and his tumor was treated with surgical resection. His tumor was found to be neuroblastoma following histological classification. The WHO classifies this neuroblastoma as histologically-defined embryonal tumors. His final diagnosis was a FOXR2 activated, CNS WHO grade 4 neuroblastoma. While these tumors are frequently associated with infants <1 year of age, there are no standard diagnostics due to the rare occurrence of these tumors in toddlers and children.[1] These tumors are often defined by their DNA methylation profile and can often be tested with immunostain OLIG2. However, as these cases are rare, molecular confirmation is often needed with sequencing for the FOXR2 transcription factor rearrangement.

Neuroblastomas have been known to affect young children and are almost exclusively located in the supratentorial region. Radiologically, neuroblastomas involve cerebral white matter and contain solid, cystic, and necrotic components. CNS neuroblastoma with FOXR2 activity is typically characterized by clusters of poorly differentiated embryonal cells.[1,4] Chromosomal rearrangement of FOXR2 transcription factor increases the expression of FOXR2, which increases interactions with myc, thus promoting tumor growth through increased transcription in cells.[1] This patient's preliminary pathology, however, disclosed few mitotic figures and a "low grade" tumor with inconclusive molecular results, which are incongruent with established information on neuroblastomas. Patients with neuroblastomas present with symptoms of mass effect.[4] The major presenting complaint for children diagnosed with neuroblastomas was headache and vomiting. This patient had seizures and some focal neurologic deficits demonstrated by his inability to ambulate for 1 day.

Due to non-specific symptoms of tumor mass effect along with the patient's age and MRI results, CNS neuroblastoma had to be distinguished from other CNS tumor etiologies. Thus, the patient was treated with tumor resection and histological definition, which revealed CNS neuroblastoma.

CONCLUSION

This case highlights the rare presentation of a CNS neuroblastoma with FOXR2 activated with pathology demonstrating an absence of high-grade features typically seen in CNS neuroblastoma with FOXR2 activated. We present this case in hopes of promoting further understanding of the different pathologic presentations of pediatric brain tumors. An absence of the features seen in the CNS neuroblastoma outlined in this case highlights the need for further research to understand better how CNS neuroblastoma can present.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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