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(CASE REPORT)

Pediatric Central Nervous System Neuroblastoma with Suspected FOXR2 Activation Mimicking a High-Grade Glioma: A Case Report and Review of the Literature

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Abstract

Central nervous system neuroblastoma with FOXR2 activation (CNS NB-FOXR2) is a recently recognized and exceptionally rare embryonal tumor entity predominantly affecting children. Owing to its nonspecific clinical, radiological, and histopathological features, preoperative diagnosis remains particularly challenging. We report the case of a 10-year-old child presenting with progressive left hemiparesis, generalized tonic–clonic seizures, and signs of intracranial hypertension. Brain magnetic resonance imaging revealed a large heterogeneous right frontal supratentorial lesion with solid, cystic, and hemorrhagic components, initially diagnosed as a pediatric high-grade glioma on stereotactic biopsy. Following ventriculoperitoneal shunt placement for hydrocephalus, the patient underwent microsurgical tumor resection. Histopathological analysis was consistent with an embryonal tumor suggestive of FOXR2-activated CNS neuroblastoma, while molecular studies were recommended for definitive characterization. Postoperatively, neurological improvement was observed; however, follow-up imaging demonstrated persistent infiltrative tumor progression without spinal dissemination. This case highlights the diagnostic complexity of CNS NB-FOXR2 tumors and underscores the importance of integrating histopathological and molecular analyses for accurate diagnosis and therapeutic planning in pediatric supratentorial tumors

Keywords: CNS neuroblastoma; FOXR2 activation; Pediatric brain tumor; Embryonal tumor; Supratentorial lesion

1. Introduction

Central nervous system neuroblastoma with FOXR2 activation (CNS NB-FOXR2) is a recently recognized molecular entity within the spectrum of embryonal tumors of the central nervous system. These tumors are characterized by recurrent genetic alterations and a highly consistent DNA methylation profile. Historically, many lesions currently classified as CNS NB-FOXR2 were previously grouped under the category of primitive neuroectodermal tumors (PNETs), a classification that has been abandoned in the most recent World Health Organization (WHO) classification of central nervous system tumors owing to advances in molecular profiling. Despite these developments, CNS neuroblastoma remains an exceptionally rare and incompletely characterized entity, with limited data regarding its clinical presentation, imaging features, histopathological spectrum, and optimal therapeutic management.

Radiologically, CNS NB-FOXR2 tumors most commonly present as large supratentorial masses in the pediatric population and may demonstrate heterogeneous imaging characteristics, including cystic, necrotic, hemorrhagic, and contrast-enhancing components. Because these radiological findings are nonspecific and frequently overlap with those of other aggressive pediatric brain tumors, establishing a definitive preoperative diagnosis remains particularly challenging. Histopathological examination, supported by immunohistochemical and molecular analyses, therefore remains essential for accurate diagnosis and classification.

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Herein, we report a rare case of pediatric CNS neuroblastoma with suspected FOXR2 activation presenting as a large frontal supratentorial lesion initially diagnosed as a pediatric high-grade glioma on stereotactic biopsy. We highlight the diagnostic challenges, radiological and histopathological findings, surgical management, and therapeutic considerations, together with a review of the relevant literature.

2. Case Report

A 10-year-old child with no significant past medical history presented with a several-month history of progressive weakness initially involving the left upper limb and subsequently the left lower limb, resulting in left-sided hemiparesis (muscle strength graded 3/5). The clinical course was further marked by the onset of generalized tonic–clonic seizures, prompting admission to another institution, where the patient underwent brain magnetic resonance imaging (MRI) and stereotactic biopsy. Histopathological findings from the biopsy were suggestive of a pediatric high-grade glioma.

On admission to our department, neurological examination revealed a conscious patient with a Glasgow Coma Scale (GCS) score of 15. Pupils were equal and reactive to light. The patient presented with a left pyramidal syndrome associated with grade III left facial palsy and recurrent generalized tonic–clonic seizures. Additional symptoms included dizziness, headache, and multiple episodes of vomiting. Fundoscopic examination demonstrated grade III papilledema, suggestive of intracranial hypertension.

A computed tomography (CT) scan revealed hydrocephalus with transependymal cerebrospinal fluid resorption(figure1) . A ventriculoperitoneal shunt was therefore placed. Cerebrospinal fluid (CSF) analysis was unremarkable, and postoperative radiographic evaluation confirmed appropriate intracranial and abdominal positioning of the shunt catheter. Following the procedure, the patient showed clinical improvement, with resolution of headache and vomiting.

Subsequent brain MRI demonstrated a right frontal supratentorial mass with a superficial leptocortical location measuring approximately 52 × 47 × 47 mm. The lesion exhibited marked surrounding infiltrative changes and was composed of two distinct components: a solid tissue portion and a multiloculated cystic component. The solid component, internal septations, and cyst wall demonstrated intermediate signal intensity on both T1- and T2-weighted sequences, associated with diffusion restriction and intense heterogeneous enhancement following gadolinium administration. An intralesional hemorrhagic component with a fluid–fluid level was also observed. Magnetic resonance spectroscopy revealed a markedly elevated lipid–lactate peak, an increased choline-to-creatine ratio (approximately 4.6), and complete loss of the N-acetylaspartate (NAA) peak.(figure 1)

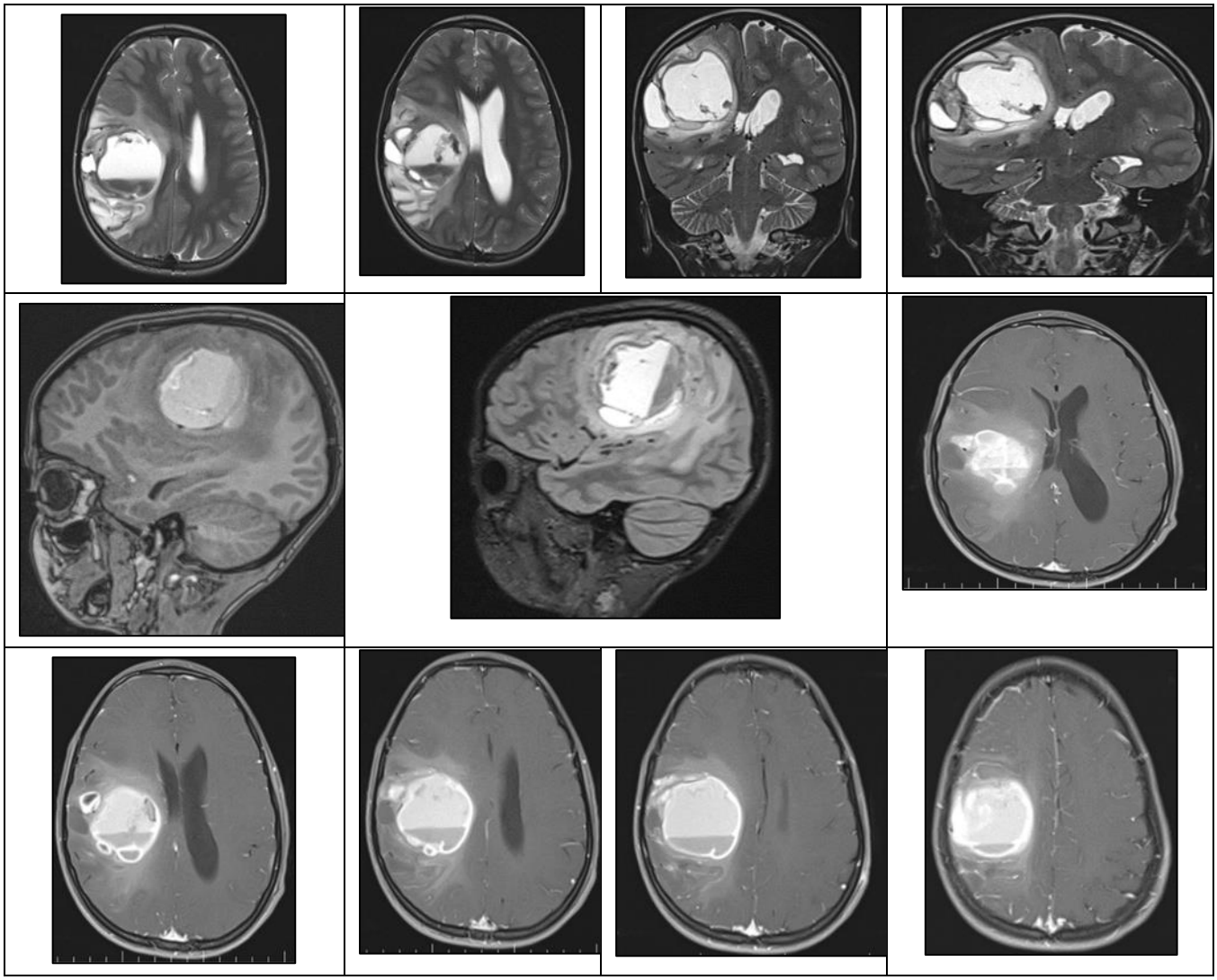

Figure 1 Brain MRI demonstrating a right frontal superficial leptocortical supratentorial mass, composed of a solid enhancing component and a multiloculated cystic portion. The lesion exhibits marked perilesional infiltration, with the solid component, cyst wall, and internal septations showing intermediate signal intensity on T1- and T2-weighted images, associated intense heterogeneous gadolinium enhancement. An intralesional hemorrhagic component with a fluid–fluid level is also identified

The case was discussed during our multidisciplinary neuro-oncology meeting, and surgical resection was recommended.

Tumor resection was performed under general anesthesia. Initial extradural puncture of the cystic component yielded approximately 30 mL of dark brown fluid with a characteristic “motor oil” appearance. Microsurgical tumor resection subsequently revealed a grayish lesion with heterogeneous consistency, partially friable and suctionable in certain areas while firm and fibrous in others, associated with marked hemorrhagic tendency. Careful dissection of the tumor capsule was performed, and tissue specimens were sent for histopathological examination. ((figure 2). Intraoperatively, the patient received one unit of packed red blood cells and two units of fresh frozen plasma. Postoperatively, the patient was extubated without complications and transferred to the neurosurgical ward in stable condition, remaining conscious (GCS 15) with persistent left hemiparesis graded 3/5. Medical management included analgesics, corticosteroids, antiepileptic therapy, and supportive treatment. A postoperative CT scan performed 6 hours after surgery confirmed satisfactory tumor resection. (figure 3)

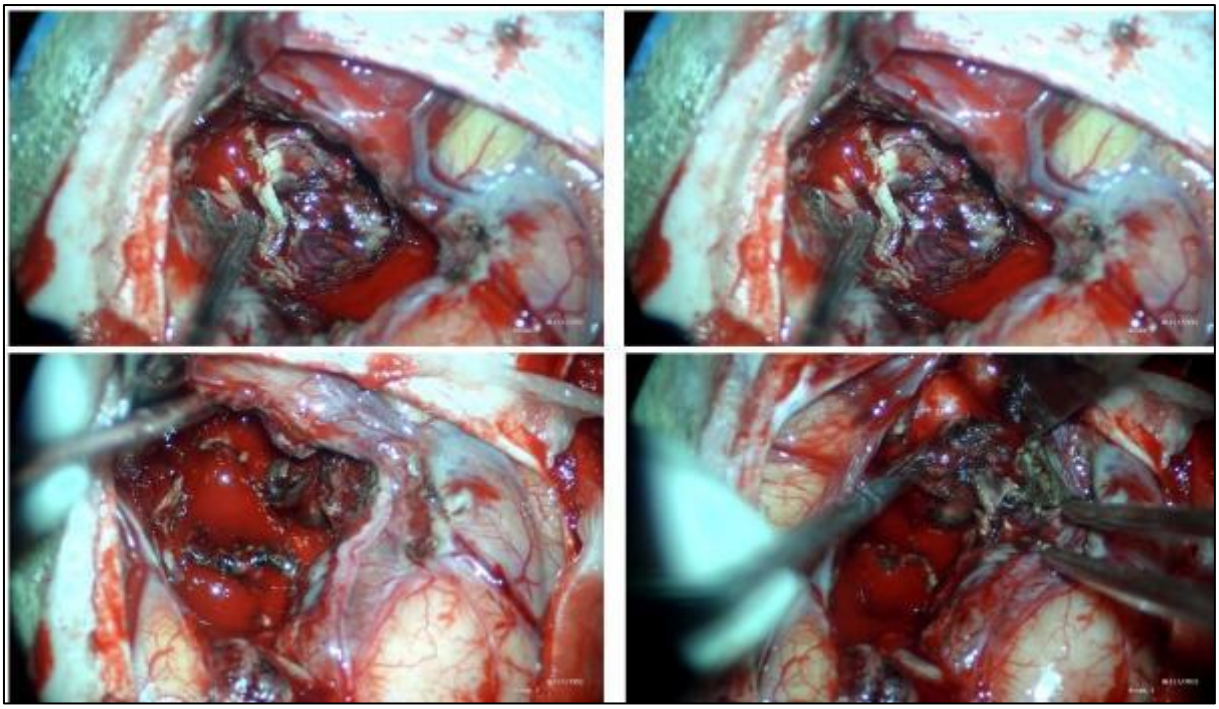

Figure 2 Intraoperative microscopic photographs illustrating tumor resection. The lesion exhibited a grayish appearance with marked vascularity and hemorrhagic tendency, associated with heterogeneous consistency, including friable and suctionable regions alternating with firmer fibrous areas. Progressive microsurgical debulking and capsular dissection are demonstrated

Throughout hospitalization, the patient underwent intensive physiotherapy, resulting in marked neurological improvement, with left hemiparesis improving from 3/5 to 4+/5 and no further seizure episodes.

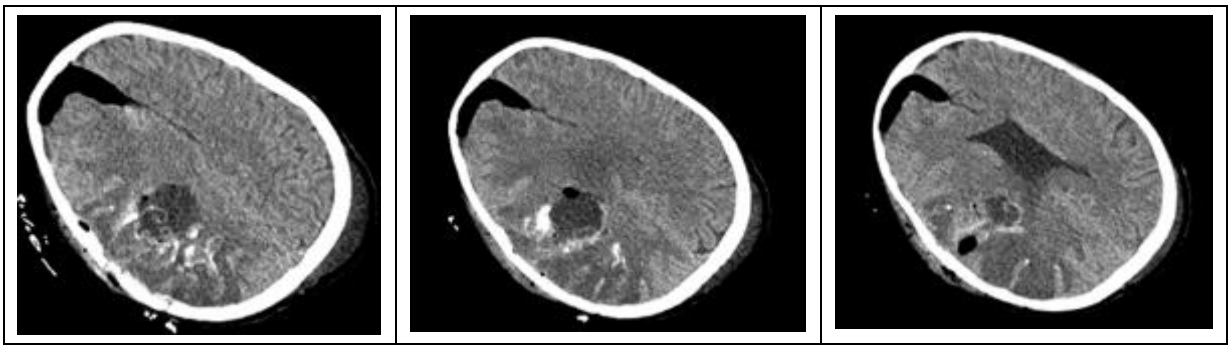

Figure 3 Early postoperative brain CT scan demonstrating the tumor resection cavity with satisfactory extent of resection, associated with postoperative hemorrhagic changes within the surgical bed

Histopathological analysis was consistent with an embryonal tumor suggestive of FOXR2-activated central nervous system neuroblastoma, while embryonal tumor, not otherwise specified (NOS), remained within the differential diagnosis. Molecular studies were recommended for further characterization.

The case was subsequently reviewed by the pediatric oncology team, and additional spinal and brain MRI examinations, together with molecular investigations, were requested. Three-month follow-up spinal MRI demonstrated no evidence of spinal dissemination. However, follow-up brain MRI revealed a reduction in the necrotic-hemorrhagic component of the previously identified right frontoparietotemporal lesion, now measuring 31 × 45 × 37 mm. The tumor remained composed of tissue, hemorrhagic, and cystic components with internal septations showing isointense signal intensity on T1- and T2-weighted sequences and heterogeneous post-contrast enhancement. Despite this reduction, increased cortical tumor infiltration was observed, predominantly within the frontoparietal region, extending into the right corona radiata and crossing the midline through the corpus callosum. Additional ipsilateral extension along the corticospinal tract to the level of the pons was noted, resulting in a 6-mm midline shift (figure5)

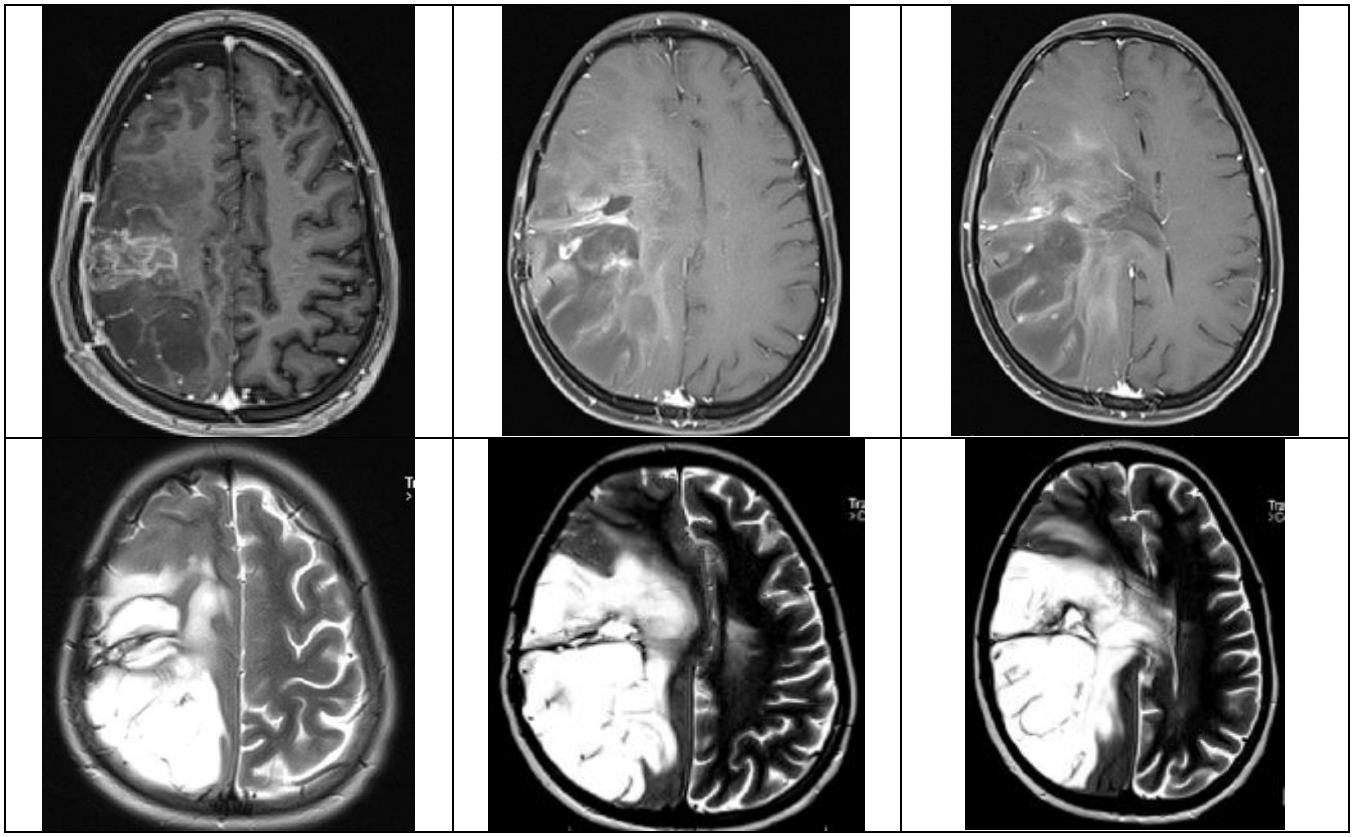

Figure 4 Follow-up brain MRI showing a reduction in the size of the necrotic-hemorrhagic component of the previously identified right frontoparietotemporal tumor, The lesion remains composed of tissue, hemorrhagic, and cystic components with internal septations, demonstrating isointense signal on T1- and T2-weighted sequences and heterogeneous post-contrast enhancement. There is progression of cortical tumor infiltration, predominantly in the right frontoparietal region, extending into the right corona radiata and crossing the midline via the corpus callosum. Ipsilateral extension along the corticospinal tract to the level of the pons is noted, associated with midline shift

The patient was subsequently referred to the pediatric oncology department for consideration of adjuvant therapy. At the time of manuscript preparation, clinical evolution and treatment outcomes remained unavailable, as management was still ongoing.

3. Discussion

CNS neuroblastoma is an uncommon tumor type that is classified within the diverse group of embryonal tumors of the central nervous system. Although it was recognized as a distinct entity in the 2016 World Health Organization (WHO) classification of CNS tumors, its diagnosis is still largely based on nonspecific histological characteristics, and clear defining molecular markers have not yet been established[1].

Because this tumor is extremely rare, available information on its epidemiology, as well as its clinical presentation and radiological features, remains limited.

Patients affected by CNS neuroblastoma are predominantly children, with the highest incidence occurring around the age of five years. A slight predominance in females has been reported. Clinically, the tumor typically manifests with symptoms associated with supratentorial mass lesions, such as headaches, vomiting, seizures, and focal neurological impairments.[2]

Radiological features are variable; however, the tumor typically appears as a large supratentorial mass and often shows cystic components as well as prominent vascular structures.[2]

The CT and MRI findings of primary cerebral neuroblastoma are more heterogeneous than previously appreciated. Several studies have demonstrated that peri- and intraventricular locations are relatively common. CT scanning appears to be more useful than non-contrast MRI at both initial diagnosis and during follow-up, particularly due to its higher

sensitivity for detecting calcifications and leptomeningeal involvement. Contrast-enhanced CT is also more effective than non-contrast MRI in distinguishing tumor recurrence from post-therapeutic changes, although postoperative enhancement and radiation necrosis may sometimes produce similar imaging appearances. Multiplanar MRI mainly contributes to better anatomical delineation of peri- and intraventricular lesions. In addition, contrast-enhanced MRI is essential for identifying tumor recurrence in surgical sites or cystic regions, as well as for detecting leptomeningeal spread. Overall, primary central nervous system neuroblastoma does not exhibit pathognomonic imaging features on either CT or MRI. Consequently, it should always be included in the differential diagnosis of intraparenchymal and juxtaventricular masses3.

CNS neuroblastoma is believed to originate from neuroectodermal cells, although the precise cell of origin remains uncertain. Histologically, the tumor typically exhibits a biphasic growth pattern composed of poorly differentiated embryonal cells arranged in compact clusters. These areas alternate with cells displaying clear cytoplasm, suggesting neurocytic differentiation, which are embedded within a fibrillary background. Similar to other embryonal tumors, features such as palisading necrosis and Homer Wright rosettes may also be observed[4–6].

In the pediatric population, supratentorial CNS tumors encompass a wide and heterogeneous spectrum of aggressive neoplasms. These include atypical teratoid/rhabdoid tumors (AT/RTs), embryonal tumors with multilayered rosettes (ETMRs), high-grade gliomas, and ependymomas. In addition, another category of embryonal tumors was historically grouped under the term primitive neuroectodermal tumors (PNETs). Although this designation was widely used in earlier classifications, advances in molecular pathology and genetic profiling have since demonstrated that these tumors represent biologically distinct entities with different clinical behaviors and prognostic implications[7,8].

In contrast to the previously mentioned tumor types, which generally exhibit well-recognized histopathological features and specific molecular or genetic alterations, the group formerly classified as PNET has long remained poorly defined. Recent advances in molecular characterization have demonstrated that these tumors are not a single pathological entity but rather a biologically diverse collection of neoplasms. Among the newly identified subtypes within this heterogeneous category is CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2), which is now recognized as a distinct molecular entity with unique biological and clinical characteristics[2,6].

Histopathological and MRI evaluations of CNS NB-FOXR2 tumors have demonstrated a remarkably broad range of microscopic and radiologic characteristics, extending far beyond the classic appearance of primitive neuroectodermal tumor (PNET)-like lesions composed of small round blue cells. On histological examination, these neoplasms may exhibit diverse features such as microvascular or endothelial proliferation, areas of necrosis, pseudorosette formation, marked nuclear atypia or pleomorphism, and pronounced vascular richness. Imaging findings are equally variable, reflecting the heterogeneity of the tumor architecture and biological behavior. Despite this morphological diversity, the most consistent finding across reported cases remains the presence of poorly differentiated embryonal-appearing cells, which constitute the common pathological hallmark of these tumors[9].

Maximal surgical resection remains the cornerstone of treatment for primary cerebral neuroblastoma (PCN-NB), with the objective of removing as much tumor tissue as safely possible. At present, no universally accepted guidelines have been established regarding adjuvant therapy for this rare neoplasm. Nevertheless, postoperative management may include chemotherapy, with or without radiotherapy, depending largely on the patient's age and clinical presentation.[10]

Several authors have emphasized the potential benefit of craniospinal or whole-brain irradiation because of the significant risk of local tumor recurrence and cerebrospinal fluid dissemination. In particular, Bennett and Rubinstein suggested that prophylactic irradiation of the brain and spinal axis could be justified in view of the tumor's propensity for metastatic spread within the neuraxis. Similarly, Lu et al. reported encouraging clinical outcomes with the use of adjuvant radiotherapy as part of multimodal treatment strategies.[4,11]

Despite these observations, the role of radiotherapy remains controversial, especially in pediatric patients, who represent the population most frequently affected by neuroblastoma. Concerns regarding long-term neurocognitive impairment, endocrine dysfunction, and developmental toxicity considerably limit the use of irradiation in young children. Owing to the exceptional rarity of PCN-NB and the limited number of reported cases, therapeutic approaches are not yet standardized, and many biological, prognostic, and therapeutic aspects of this uncommon tumor remain insufficiently understood.[12]

The therapeutic management of neuroectodermal tumors of the central nervous system (CNS-PNETs) generally follows treatment strategies comparable to those used for medulloblastomas. Standard therapy is typically based on a multimodal approach combining craniospinal irradiation (CSI) with an additional focal radiation boost directed at the

primary tumor site, together with intensive chemotherapy protocols. Chemotherapeutic regimens commonly incorporate several agents, including methotrexate, cisplatin, etoposide, topotecan, cyclophosphamide, vincristine, and, in selected cases, vinblastine. In certain clinical settings, these medications may also be administered according to metronomic schedules, consisting of prolonged low-dose continuous therapy aimed at limiting tumor progression while reducing treatment-related toxicity.

For children older than infancy, craniospinal irradiation remains a cornerstone of treatment because of the high propensity of these tumors for cerebrospinal dissemination. However, in infant patients, the benefit of CSI appears considerably more limited. Several studies have failed to demonstrate a significant improvement in survival outcomes for neuroblastoma occurring in this age group, while the potential long-term neurocognitive and developmental adverse effects of irradiation remain substantial. Consequently, therapeutic strategies in infants often prioritize intensive chemotherapy and attempts to delay or avoid radiotherapy whenever possible[13].

Because primary central nervous system neuroblastoma (PCNSN) is an exceptionally uncommon tumor, establishing reliable prognostic factors and defining optimal therapeutic strategies remain major challenges. The limited number of reported cases and the absence of large prospective studies make it difficult to accurately assess treatment outcomes or develop standardized management protocols. Consequently, most current knowledge is derived from isolated case reports, small case series, and retrospective database analyses[11].

Among the available large-scale studies, analyses based on the Surveillance, Epidemiology, and End Results Program (SEER) database have provided valuable epidemiological and prognostic insights into these rare tumors. These studies demonstrated that several factors appear to influence survival outcomes. Younger age at diagnosis, particularly during infancy, was associated with a more favorable prognosis. In addition, tumors exhibiting ganglioneuroblastoma (GNBL) differentiation tended to show improved survival compared with more poorly differentiated forms. Surgical management also emerged as a significant positive prognostic factor, highlighting the importance of maximal safe tumor resection in overall treatment strategies[14].

Conversely, the presence of distant metastatic dissemination was associated with less favorable clinical outcomes and appeared to represent a negative prognostic indicator. Tumor spread through the cerebrospinal fluid pathways or to distant intracranial and spinal sites often reflects more aggressive biological behavior and complicates therapeutic management. Despite these observations, the rarity of PCNSN continues to limit definitive conclusions, and further multicenter molecular and clinical studies are required to better characterize prognostic determinants and optimize treatment approaches for this rare pediatric neuro-oncological entity[15].

4. Conclusion

Primary CNS neuroblastoma is an uncommon and complex pathology characterized by marked variability in its clinical presentation and imaging features, which frequently resemble those of other intra-axial or juxtaventricular brain tumors. As demonstrated in this case, radiological findings are not specific and are often insufficient to establish a definitive diagnosis prior to surgery, thus requiring histopathological examination supported by immunohistochemical studies for confirmation.This report underscores the necessity of including primary CNS neuroblastoma in the differential diagnosis of pediatric intracranial tumors, especially when lesions are located in peri- or intraventricular regions. Prompt identification and accurate diagnosis are essential, as they significantly impact both therapeutic decision-making and patient prognosis. While multimodal imaging is valuable for lesion assessment, surgical planning, and follow-up, it does not provide pathognomonic features sufficient for a definitive diagnosis on its own.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

"Informed consent was obtained from all individual participants included in the study."

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