Medulloblastoma in a toddler with Gorlin syndrome

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ABSTRACT

Gorlin syndrome (GS) is a rare hereditary multisystem disorder caused by mutations in *PTCH1*, *PTCH2*, or *SUFU*. It is characterized by multiple anomalies and an increased risk of developing various tumors. Basal cell carcinoma is most common, and medulloblastoma (MB) is especially frequent in patients with *SUFU* mutations. MB treatment often includes radiation therapy in patients older than 3 years; however, such treatment is very toxic to patients with GS. Most reported cases of MB in patients with GS present after GS is diagnosed. We report a male toddler with multicentric posterior fossa tumor and calcifications along the falx cerebri, suggesting MB and GS. Pathology revealed nodular MB. His testing confirmed a germline *SUFU* mutation. His tumor resolved with three induction cycles of chemotherapy, but he died of respiratory failure due to infection at 20 months of age. Overlooking calcifications along the falx cerebri in children with MB can induce significant morbidity.

KEYWORDS Falx cerebri; Gorlin syndrome; medulloblastoma; *SUFU* mutation

Medulloblastoma (MB) is the most common malignancy of the brain in children and can be triggered by predisposing syndromes.¹ Advancements in understanding the genetic background of MB have helped in disease stratification and effective risk adoptive therapy.² Gorlin syndrome (GS) is caused by autosomal dominant mutations in *PTCH1*, *PTCH2*, or *SUFU*. It is characterized by multiple basal cell carcinomas of the skin and other neoplasms and abnormalities.³ Most patients with GS have heterozygous germline mutations in *PTCH1*, and 5% of them develop childhood MB. However, those with *SUFU*-related GS have a much higher risk for MB.⁴ Mutations in *SUFU* are associated with nodular/desmoplastic subtype MB in the toddler years.^{4,5} Other characteristic findings in *SUFU*-related GS include falx calcifications, sensitivity to radiation and subsequent second primary tumors in the radiation fields, and a strong family predisposition.^{4,5}

CASE REPORT

A 16-month-old biracial male was hospitalized with progressive bilateral esotropia that was worse on the right. He also had loss of appetite, clumsiness, and imbalance with crawling. The patient started cruising without walking at 15 months of age but progressively digressed with onset of ataxia. His medical history included a nuchal cord during pregnancy, full-term

delivery, and a brief stay in the neonatal intensive care unit at birth due to respiratory distress but without the requirement for intubation. He met all developmental milestones except for walking and had no notable cognitive impairment. Significant family history included a half brother with cerebral palsy, hydrocephalus, and a possible brain mass who died at 3 years of age.

Neuroimaging revealed a multicentric tumor in the posterior fossa, positive leptomeningeal spread, and punctate calcifications along the falx cerebri. A probable diagnosis of MB in a child with GS was suggested (*Figures 1 and 2*). Upfront subtotal resection was performed and a histologic diagnosis consistent with MB, nodular type was rendered.

Our patient fulfilled two major diagnostic criteria for the diagnosis of GS (*Table 1*).⁶ Genetic testing confirmed the presence of the p.R146* nonsense pathologic mutation in the *SUFU* gene. After subtotal resection, our patient received chemotherapy per protocol CCG-99703.⁷ Therapy included three induction cycles with a plan for high-dose chemotherapy and rescue auto stem cell transplantation. Auto stem cell harvest was unsuccessful, and high-dose chemotherapy could not be administered after induction was completed. He experienced respiratory failure due to chronic severe rhinovirus infection and ill-defined pulmonary vascular hypertension. After weeks on maximal life support, and despite his remission from MB,

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Figure 1. Computed tomography of the head without contrast showing a sagittal posterior fossa mass and calcification along the falx cerebri.

Table 1. Criteria for Gorlin syndrome		
Type	Criteria	Our patient
Major	Multiple (>2) basal cell carcinomas or one diagnosed under 20 years	No
	Medulloblastoma, typically desmoplastic/nodular type	Yes
	Odontogenic keratocysts proven by histology	No
	≥3 palmar or plantar pits	No
	Ectopic calcification (lamellar or early falx)	Yes
	Family history of NBCCS	Questionable
Minor	Skeletal malformations (sella turcica, vertebral, hands and feet)	No
	Ocular anomaly (cataract, coloboma, microphthalmia)	No
	Rib anomalies	No
	Macrocephaly	No
	Cleft lip or palate	No
	Cardiac or ovarian fibroma	No
	Lymphoepithelial cysts	No

NBCCS indicates nevoid basal cell carcinoma syndrome. A diagnosis of Gorlin syndrome requires (1) one major criterion and molecular confirmation; (2) two major criteria; or (3) one major and two minor criteria.⁶

Figure 2. (a, b) Magnetic resonance imaging (MRI) postcontrast T1 sequence shows multifocal enhancing mass in the posterior fossa prior to resection. (c) MRI diffusion-weighted imaging image shows abnormal restricted diffusion within the posterior fossa mass prior to resection. (d) MRI diffusion tensor imaging with fiber tracking shows relationship of the middle cerebellar peduncles (green fibers) with the tumor in the posterior fossa.

he succumbed to respiratory failure at 20 months of age. Autopsy did not reveal residual tumor.

DISCUSSION

Patients with GS have physical features that often result in making the diagnosis.⁶ Basal cell tumors affect 50% of children with GS, but a much smaller minority develop other tumors. Those tumors are mostly mesenchymal hepatic tumors and MB. Only 5% of children with GS develop MB. Nevertheless, *SUFU*-related GS has a 20 times higher risk for MB than *PTCH1*-related GS, and most MB cases have affected infants.⁴

With better understanding of the biology of MB, the disease has been divided into four groups with distinct biological signatures: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4. This biological background has allowed risk-based stratification. Low-risk MB includes the WNT subgroup and nonmetastatic group 4 tumors with chromosome 11 loss or 17 gain. High-risk strata include patients with metastatic SHH or group 4 tumors or *MYCN*-amplified SHH-MB. Very high-risk patients are those with group 3 with metastases or SHH with the *TP53* mutation.² Risk adoptive therapy has allowed us to reduce toxicity in low-risk groups and further our search for better targets in high-risk groups.^{8,9}

Recognizing underlying comorbidities that suggest a need for treatment modification can result in a significant reduction in treatment-related morbidity and mortality.¹⁰ Our case demonstrates the impact of early detection of GS, an MB-predisposing syndrome, on delivering optimal therapy and minimizing toxicity. Radiation is often used in treating patients with MB above 3 years of age; however, its toxicity to patients with GS can be devastating.^{3,4} Though most reported cases of GS in the literature account for MB presenting after a GS diagnosis, a small minority of patients with GS are likely to present with MB as experienced by our patient. Those patients are underreported in the literature.¹¹ Calcifications in the falx cerebri are extremely rare in pediatrics; their presence is considered pathologic and should raise suspicion for GS until ruled out. Additional findings consistent with the revised diagnostic criteria would further support the diagnosis (*Table 1*). The failure to

mobilize hematopoietic stem cells and the death of rhinovirus pneumonitis are unique in the setting of GS-associated MB; however, they are not likely related.

The rarity of coinciding GS and MB, advances in our understanding of biology, and the need for personalized medicine emphasize the need for early diagnosis by astute clinicians. In our case, radiological findings triggered appropriate genetic testing and assisted in cancer control.

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